Ф А 2.2.1-32-367

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QUALIFICATION WORK

on the topic: **«STUDY OF MODERN APPROACHES TO THE FORMATION OF REGULATORY LISTS FOR THE PROVISION OF PHARMACEUTICAL CARE TO CHILDREN"**

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Kharkiv – 2023 year

ANNOTATION

In order to ensure safe pharmacotherapy of children, it is extremely important to have children's dosage forms in the pharmacy assortment. The lack of modern drugs leads to the fact that children are often prescribed drugs based on adult forms. The work presents an overview of the diversity of the legislative and regulatory framework, which reflects the specificity of children's medicinal forms. The qualifying paper compares the Tanzania National List of Essential Medicines (2021) with the World Health Organization's List of Essential Medicines for Children (2021) on the differences between medicines and dosage forms listed for children.

Qualification work is laid out on 58 pages, consists of an introduction, 3 sections, general conclusions, a list of used sources.

Key words: essential medicines, regulation, children's medicinal forms, National List of Essential Medicines, pharmaceutical care.

АНОТАЦІЯ

Для забезпечення безпечної фармакотерапії дітей надзвичайно важливою є наявність в аптечному асортименті дитячих лікарських форм. Відсутність сучасних препаратів призводить до того, що дітям часто призначають препарати, виготовлені на основі дорослих форм. У роботі представлено огляд розмаїття законодавчої та нормативно-правової бази, що відображає специфіку дитячих лікарських форм. У кваліфікаційній роботі порівнює Національний список основних лікарських засобів Танзанії (2021) зі Списком основних лікарських засобів для дітей Всесвітньої організації охорони здоров’я (2021) щодо відмінностей між лікарськими засобами та лікарськими формами, перерахованими для дітей.

Кваліфікаційна робота викладена на 58 сторінках, складається із вступу, 3 розділів, загальних висновків, списку використаних джерел.

Ключові слова: основні лікарські засоби, регулювання, дитячі лікарські форми, Національний перелік основних лікарських засобів.

CONTENT

ABBREVIATIONS

ANAM – National Health Insurance Agency

EMA – European Medicines Agency

EML - Essential Medicines List

EMLc - Essential Medicines List for children

EU-European Union

EC - European Commission

FDA – Food and Drug Administration

FIP - International Pharmaceutical Federation

GMP – Good Manufacturing Practice

ICESCR - International Covenant on Economic, Social and Cultural Rights

MENA - Middle East and North Africa

MP - Medical Products

NMRAs - National medicines regulatory authorities

NHS - National Health System

NDP - National Drug Policy

NDR - National Drug Registry

NEMLs - National Essential Medicines Lists

OPs – Online Pharmacy

OTC - Over-the-counter

PC - Pharmaceutical Care

POM - Prescription-only medicines

HTA – Health Technology Assessment

OECD – Organisation for Economic Cooperation and Development

RAs - Regulatory authorities

WHO - World Health Organization

INTRODUCTION

Relevance of a subject. Rational pharmacotherapy in children remains one of the most urgent problems in medicine and pharmacy. The problem of this issue is the ignoring of the ethical and deontological principles of pediatric pharmacology, namely: numerous drugs that are used in adults, by the same analogy, are used in children's practice, which, accordingly, is unacceptable in the conditions of the modern level of pharmacy development. The absence of registered children's medicinal forms leads to the prescription of medicines "off-label" ("outside the instructions"), in violation of the prescriptions of the approved instructions. It has been established that the child's body has a number of anatomical and physiological features, which most often determine its difference (compared to an adult) reaction to the introduction of xenobiotics, including drugs. Therefore, the principles of treatment and prevention of pathological conditions in childhood recommended for adults are not always effective and justified and require a balanced approach. In 2019, an estimated 5.2 million children under 5 years old died mostly from preventable and treatable causes. The leading causes of death in children under 5 years of age are preterm birth complications, birth asphyxia/trauma, pneumonia, congenital anomalies, diarrhea and malaria. However, more than half of deaths associated with the potential complications can be prevented or treated with access to medicine treatment. Unfortunately, the availability of medicines for children is low.

The WHO Model List of Essential Medicines was launched in 1977 to make the most necessary drugs available to populations whose basic health needs could not be met by the existing supply system. During the first 30 years of the Model List of Essential Medicines, children’s needs were not systematically considered. After adoption of the ‘Better medicines for children’ resolution by the World Health Assembly, things changed. The first WHO Model List of Essential Medicines for Children was drawn up by a Paediatric Expert Subcommittee and adopted in October

2007 [47]. The most recent, 8th Model List of Essential Medicines for Children was adopted in 2021.

The purpose and tasks of the research. The purpose of the qualification work is to research modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children.

To achieve this goal, it is necessary to solve the following tasks:

- analyze the current state of pharmaceutical care for children;
- analyze the legislative acts regulating the development and implementation of medicinal forms in the world;
- to conduct a comparative analysis o between the World Health Organization list of essential medicines for children (8th list, 2021) and the Tanzania list of essential medicines (sixth edition 2021).

The subject of the study is State register of health care products of Tanzania; the legislative framework of the EU countries, the USA in accordance with the regulation of the introduction of drugs for children; Tanzania's National List of EMs, WHO List of EMs for Children, BNDF.

The objects of the study were:

- WHO regulatory orders, EU and US guidelines;
- range of drugs used in the treatment of children in Tanzania;
- legislative and normative acts regulating children's medicinal forms.

Methods of researches. The research used a system-overview, analytical and structural-logical methods of analysis.

The practical significance of the work. The purpose of this study is to critically compare NDLIM 2021 with LEMC 2021.

Scientific novelty. Delineating the absence of drugs in the list, to outline the necessary directions to stimulate this area.

Structure and volume. The qualification work consists of the introduction, three chapters, conclusions and the list of the studied literature. The total amount of the qualification work makes 58 pages of the text, including 15 tables and 9 drawings. The bibliography contains 55 names of the studied literature.

CHAPTER 1. STUDY OF PROBLEM ASPECTS IN THE PROVISION OF PHARMACEUTICAL CARE TO CHILDREN.

1.1 Analysis of features and age restrictions in prescribing drugs for children in pediatric practice.

During the last decades, the problem of pharmacotherapy in children's practice remains one of the most relevant and acute for medicine and pharmacy [1-6]. This is most often due to the fact that when choosing pharmaceuticals, ethical and deontological principles of pediatric pharmacology are underestimated or completely ignored, namely: numerous drugs that are used in adults are, by the same analogy, used in children's practice, which, accordingly, is unacceptable in the conditions of the current level of pharmacy development.

A child's body has a number of anatomical and physiological features, which most often determine its difference (compared to an adult) reaction to the introduction of xenobiotics, including medicines. Therefore, the principles of treatment and prevention of pathological conditions in childhood recommended for adults are not always effective and justified and require a balanced approach [15].

Today, numerous authors have highlighted a number of features of the child's body that affect the kinetics and metabolism of drugs in different age groups, which cannot but be reflected in the pharmacotherapeutic effectiveness [5, 7-11]. Such features include, first of all, the specificity of absorption, which is determined by the pH values of gastric juice, the state of motility of the gastrointestinal tract, the permeability of the mucous membranes of the gastrointestinal tract.

In addition, the low binding capacity of liver proteins (ligandins) and blood plasma is known, which increases the free (active) fraction of medicinal substances and causes the correction of the dosage regimen of drug use. The relative advantage of extracellular fluid, which determines the characteristics of the distribution of both water-soluble and fat-soluble medicinal substances in the child's body, has been established. It is important to note the increased permeability of the membrane structures of capillaries, the blood-brain barrier, which affects the nature and level of distribution of medicinal substances in organs and tissues and requires special

attention during infusion therapy. Also, the slow rates of functioning of enzyme systems that transform xenobiotics into inactive and water-soluble forms (system of microsomal oxidation of cytochrome P-450-oxidase of the liver, enzyme systems of glutathione reductase, glutathione transferase, uridine diphosphate glucose-glucuronyl transferase, etc.) lead to the accumulation of the active medicinal substance in the body [25-35; 44-48]. At the same time, the low levels of glomerular filtration (30-40% of the level of an adult organism), tubular secretion and reabsorption, which slow down the processes of the elimination of drugs and their metabolites, also contribute to the retention and accumulation of drugs in the body.

The immaturity of hormonal systems, including a low level of catecholamines, along with the reduced sensitivity of tissue receptors to hormones, hormone-like and other substances with a pronounced biological effect, requires a special approach to hormone and anti-inflammatory pharmacotherapy in children [12; 21].

Thus, all this determines the specificity of absorption, binding of medicinal substances at the stage of their biotransport, distribution in the body, and also determines the rate of metabolism and excretion.

It is known that the body of a child, especially one of early age, is characterized by the immaturity (or absence) of a number of enzyme systems that play an important role in the biotransformation of many medicinal substances. In particular, the monooxygenase system in newborns and young children is so weak that the half-life of euphilin is 100 h, while in an adult it is only 6; the half-life of chloramphenicol after administration of the drug in a dose of 5-25 mg/kg is on average 26 hours in infants and only 4 hours in children aged 5 years [8].

Some medicinal substances are little inactivated in children's bodies (levomycetin), others (salicylates, paracetamol) - actively. It is important to emphasize that the metabolism of paracetamol in children is significantly different from adults: as a result of biotransformation, the formation of toxic metabolites does not occur, which is caused by the immaturity of cytochrome P-450 [8, 12].

It was established that the elimination of some drugs occurs more slowly (tetracycline, urea) than in adults, the elimination of others (penicillin) is similar to

that in adults. It should be noted that the catabolic effects of glucocorticoids are more pronounced in the child's body, and the metabolic products of anabolic steroids are more toxic. Ganglioblockers practically do not change the level of blood pressure in children under 3 years of age [8].

Slow biotransformation explains the fact that children are quite sensitive to drugs that contain nitric acid anions (silver nitrate), as well as to anesthesin, phenacetin, and sulfonamides, which can lead to methemoglobinemia with long-term use. Insufficient activity of the coenzyme a system determines the development of allergic reactions to sulfonamide drugs and contributes to the formation of Reye's syndrome, which is manifested primarily by toxic encephalopathy and fatty degeneration of the liver.

At the same time, prolonged sulfonamides are much more toxic for children (liver damage, exudative polymorphic erythema of mucous membranes, etc.) [8, 13, 14].

The low concentration of protein in the blood plasma of infants and children of the first years of life (46-52 g / l compared to 72-80 g / l in adults) leads to an increase in the free fraction of the medicinal substance and the development of side effects and toxic effects from usual therapeutic doses. It is this fact that causes high toxicity and hyperbilirubinemia, which rapidly develops against the background of taking salicylate derivatives, sulfonamides, nitrofurans, local anesthetics, as well as caffeine [8, 15; 33-36].

When discussing the issue of the safe use of drugs in children, one cannot ignore the age-related dynamics of the level of permeability of the blood-brain barrier (BBB), which determines the degree of distribution of the latter in the cerebrospinal fluid and the central nervous system. It is known that in childhood, the blood-brain barrier is well permeable to the vast majority of xenobiotics, in contrast to adults. Thus, it was established that methylene blue, potassium chloride, phosphorus, glutamic acid, phenobarbital, morphine, and bilirubin easily diffuse through the BBB at an early age [7-9]. This circumstance must be taken into account when prescribing these drugs in children's practice [22].

It is important to remember that drugs can affect the fetus if the pharmacologically active ingredients are able to penetrate the placental barrier. In this area, attention is drawn to the teratogenic properties (especially in the first three months of pregnancy) of a number of drugs (antitumor, narcotic, hypnotics, anesthetics, antithyroid, sulfonamides, antibiotics of the tetracycline group, aminoglycosides, chloramphenicol), which bind poorly with blood proteins due to their resistance to the processes of dissociation, ionization or specific physical and chemical properties (fat-soluble substances with a small molecular weight). Antihistamines, natural and synthetic corticosteroids, corticotropin, salicylates, caffeine have a teratogenic effect. Ethanol even in low concentrations causes "fetal alcohol syndrome", which is characterized by congenital defects and disorders of mental and physical development of children [54-59].

Taking drugs by a pregnant woman can also cause a toxic effect on the fetus, which is manifested already after its birth (salicylates cause hemorrhagic hemorrhages, deafness can develop against the background of taking aminoglycoside antibiotics, etc.).

An example can also be side reactions to diethylstilbestrol, which is prohibited for use precisely because of its delayed teratogenicity. In the literature, the term "behavioral teratogenicity" is known, which implies that one of the causes of antisocial behavior of adolescents is the taking of certain drugs by a woman during pregnancy [5, 7-9, 12-15].

During breastfeeding, medicinal substances can enter the child with mother's milk. At the same time, it is important to know which drugs are excreted in breast milk, and which are not. Both metabolites (sibazone, chloramphenicol, isoniazid) and pharmacologically active compounds (aminazin, phenobarbital, diphenine, reserpine, propranolol, acetylsalicylic acid, neodicumarin, penicillins, tetracycline) can get into the body of a child and have a pharmacological effect similar to that in adults. , furosemide, narcotic analgesics, ethanol). It is known that high concentrations of tetracycline and chloramphenicol accumulate in breast milk, which have a toxic effect on the bone tissue and blood composition (aplastic anemia)

of the child. It is also important to remember that some drugs (penicillin, aminoglycosides) penetrate well into breast milk, but after getting to the child through the mouth, they are not absorbed in the gastrointestinal tract [8, 16-19].

Based on the risk of developing side effects in infants, a number of drugs (paracetamol, phenacetin-containing drugs, nalidixic acid, lithium salts, radioactive calcium salts, iodine, atropine, anticoagulants, antithyroid drugs, antimetabolites, bromides, tetracycline, narcotic analgesics, metronidazole) for pregnant women are contraindicated.

Caution is also necessary when prescribing barbiturates, rauwolfia drugs, ergots, diazepam, gold drugs, salicylates, as well as laxatives, sulfonamides [1, 17-19; 23].

In recent years, pharmacologists and clinicians emphasize the importance of rational dosing of medicines used in children's practice. Given that each period in a child's life is different in its features of the formation of the nervous, endocrine, muscular, cardiovascular and other systems, it is necessary to calculate the optimal dose of xenobiotics in order to obtain the desired reaction to the drug. To date, general principles of drug dosing have been developed taking into account the level of reactivity of the body, namely: calculation of the drug by weight, age of the child, as a "part of the adult dose", by the dose factor, the volume of distribution and the surface of the child's body, etc. [2-4; 30-31].

Thus, during the pharmaceutical development of drugs in pediatric practice, it is necessary to take into account the peculiarities of the pharmacodynamics and pharmacokinetics of the active substance in children of different age groups, as well as the possibility of side effects of the latter. Based on these considerations, it is quite significant to correct the doses of drugs taking into account the features of the ontogenetic development of the child, anatomical and physiological features, as well as the nature and degree of severity of the pathological process [18-22].

In tabl. 1.1. data on medicinal products that have age restrictions when prescribed to children are presented.

Table 1.1

Analysis of drugs with age restrictions when prescribed to children

Drug	**Not assigned to children**
Adiurecrine	Up to 3 years
Amifurin	Up to 5 years
Antastman (tablets)	Up to 2 years
Bactrim (Biseptol)	Premature babies and babies
Beroxan	Up to 5 years
Bucarban	In childhood and adolescence
Butamide	In childhood and adolescence
Bromhexine	Up to 3 years
Voltaren (diclofenac)	Up to 6 years
Glibenclamide (mininyl)	In childhood and adolescence
Glucobay	Persons under 18 years old
Dicain	Up to 10 years
Ditilin	Infancy
Liquid balm "Kim"	Up to 5 years
Doxycillin hydrochloride (vibramycin)	Up to 8 years
Indomethacin (methindole)	Up to 14 years
Imodium	Up to 1 year
Iodine alcohol solution (inside)	Up to 5 years
Potassium arsenite solution	Up to 2 years
Potassium gluconate	Intramuscularly
Kameton	Up to 5 years
Camphomen	Up to 5 years
Acid nalidixova (negram, nevigramon)	Up to 2 years
Oxolinic acid (gramurin)	Up to 2 years
Codeine	Up to 2 years
Codeine phosphate	Up to 6 months

Continuation of the table 1.1

Caffeine	Up to 2 years
Cromolin-sodium (intal)	Up to 5 years
Levodopa	Up to 12 years
Mazindol (terenak)	Up to 12 years
Ointment "Dermazin"	Newborns and premature babies
Menthol in nasal drops	Early age
Morphine Hydrochloride	Up to 2 years
Arsenic preparations	Up to 2 years
Nakom	Up to 12 years
Naprosin (naproxen)	Up to 16 years
Naphthyzinum	Infancy
Omnopon	Up to 2 years
Pyroxan	Up to 6 months
Piracetam (pellets)	Up to 1 years
Aniline patch	Up to 1 year
Poteseptil	Premature babies and newborns
Prazosin	Up to 12 years
Promedol	Up to 2 years
Psoberan	Up to 5 years
Psoralen	Up to 5 years
Ranisan (ranitidine)	Up to 14 years
Reopirin	Up to 7 years, after 7 years – appointed in hospital emergencies
Rifampicin	Infancy
Strychnine nitrate	Up to 2 years
Sulfatone	Premature babies and babies
Tarivid	Children and adolescents with incomplete skeleton formation
Theofedrine (tablets)	Up to 2 years
Theophylline	Up to 2 years
Tetracycline	Up to 8 years
Thymol	Up to 2 years
Triethylperazine (torecane)	Up to 15 years
Cefazoline (kefzol)	Premature babies and newborns
Cimetidine(cynumed)	Up to 7 years
Emetine hydrochloride	Up to 6 months
Ethacric acid (uregite)	Up to 2 years
Ethylmorphine hydrochloride (dionine)	Up to 2 years

In order for pharmacotherapy in children to be safe, it is first of all important to take into account the age characteristics of the child. The paediatric population represents a spectrum of different physiologies, and children should not be treated as “miniature men and women” (Abraham Jacobi, 1830-1919). The spectrum extends from the very small preterm newborn infant to the adolescent. The internationally agreed, and to some extent arbitrary, classification of the pediatric population. According to the data provided in the international document "Registration of Medicinal Products for Humans", there are 5 main periods of childhood (fig.1.1) [37].

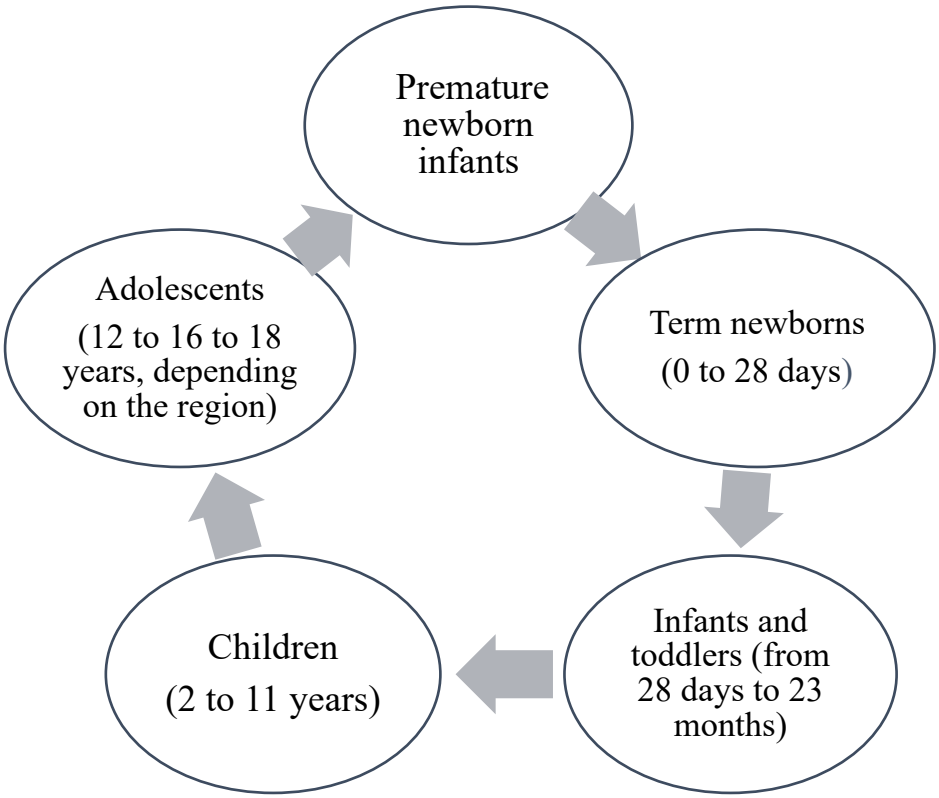

Fig.1.1 The main periods of childhood.

Substantial changes in body proportions and composition accompany growth and development. This dynamic process of maturation is one of the differences 4 between the pediatric and the adult populations. The developmental changes in physiology and, consequently, in pharmacology, influence the efficacy, toxicity and

dosing regimens of medicines used in children. It is, therefore, important to review the relevant changes that take place from birth through to adolescence.

Given the fact that pharmacotherapy, including in pediatric practice, is based primarily on the assessment of the safety of medicines, certain aspects of pharmacological correction of diseases in pediatrics have their own characteristics. Thus, antibacterial therapy is based on the principle of "soft regime".

The use of certain groups of highly active antibiotics (tetracycline, aminoglycosides) and chemotherapeutic agents (fluoroquinolones) in pediatric practice is limited [16;36].

The results of recent studies indicate an acceptable safety profile and high efficacy of ibuprofen and paracetamol. The recommended doses of paracetamol and ibuprofen for children under 12 years old are 60 mg/kg/day and 5-20 mg/kg/day, respectively. The use of widely known acetylsalicylic acid in pediatric practice is limited. It is important to emphasize that acetylsalicylic acid is contraindicated in children with or suspected of a viral infection due to possible damage to the gastric mucosa and the development of Reye's syndrome, the mortality rate of which exceeds 50% [63].

When developing drugs for the treatment of acute intestinal infections, it should be borne in mind that Shigella spp., Salmonella typhi, and Vibrio cholerae are included in the list of pathogens that warrant antibacterial therapy. Based on the fact that pathogen strains are currently resistant to traditional drugs (tetracycline, chloramphenicol, nalidixic acid, ampicillin, cotrimoxazole), it is rational to carry out pharmacological correction with semisynthetic penicillins with predominant activity against gram-negative pathogens, as well as macrolides (azithromycin) [68]. At the same time, the program of therapy for diarrheal syndrome in children includes not only the use of enterosorbents, but also medical nutrition (fermented milk products, dietary fibers), microbiological correction (pre- and probiotics, bacteriophages), and also involves the appointment of immunomodulators (viferon, sodium nucleate, lycopid and etc.) [57, 68].

To date, it has been established that in the case of gastroduodenal diseases, the drugs of choice for children's practice are rather mild drugs containing magnesium (maalox), which reduce the intensity of microbial colonization of the upper parts of the digestive tract by increasing the resistance of the mucous membrane of the stomach and intestines. Eradication of Helicobacter pylori in children under 12 years of age is recommended using furazolidone and furagin, which are highly effective in contrast to the traditionally used metronidazole, to which microbial resistance has developed.

Given the anatomical and physiological features of the skin of infants and children of younger age groups (primarily high bioavailability of xenobiotics when administered transdermally), it is not recommended to include substances with a toxic effect (boric acid) that contribute to the acceleration of exfoliation processes that change its permeability, disrupt heat and gas exchange (salicylic acid, hydroxy acids, petroleum jelly, paraffin, lanolin, etc.), and also have an irritating effect (menthol, potassium permanganate) [31].

The problem of polypharmacy is particularly relevant in pediatrics: the risk of complications increases when several drugs are prescribed at the same time against the background of physiologically determined slowed metabolism.

So, to date, it has been established that in the case of combined therapy with antibiotics, antipyretics, antihistamines and immunostimulatory against the background of viral diseases, the percentage of allergy is much higher than with the separate use of chemotherapeutic agents in the treatment of bacterial infections. It has been established that some drugs affect the assimilation and biotransformation of vitamins, especially fat-soluble vitamins. Yes, it is known that laxatives, cholestyramine and similar lipid-lowering drugs disrupt the absorption of vitamins A, D, E; anticonvulsants, antibiotics used to eradicate N; pylori significantly change the metabolism of vitamin K and other water-soluble vitamins [58].

1.2 Analysis of the features of the development of medicinal forms for children.

Considerations for prescribing medications in pediatrics include: whether the drug is safe and approved for use in children; what the appropriate dose is for the child's age and weight; and, what key information about adverse reactions needs to be communicated to the parent or caregiver.

Children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in ensuring the drug prescribed is appropriate and that the correct dosage is given, especially in the neonatal period.

Currently, the following basic requirements for children's medicines are established (fig.1.2).

Requirements	High therapeutic efficiency and high bioavailability;
	Pleasant organoleptic properties
	Polycomponent;
	Sterility (for newborns);
	Stability;
	Pyrogenicity (for newborns); No allergenic effect; Microbiological purity; Ease of use; Non-toxicity
	They should provide a positive psychological and physiological influence on the child(type of dosage form, color, taste, effect, smell) - it is preferable not to use injections.

Fig.1.2 Basic requirements for children's medicines.

Pharmacotherapy in pediatrics allows the use of drugs in standard dosage forms (capsules, tablets, ointments, suppositories, solutions for parenteral

administration, eye and nasal drops, collections, etc.). However, the current level of development of medicine requires the use of pharmaceuticals in the form of special children's dosage forms that provide age-specific dosage of the active substance, efficiency and ease of use. Today, in pediatric practice, drugs in the form of adjusted syrups, suspensions, lozenges, water-soluble powders, granules and tablets with a pleasant taste are widely used [24-26; 37-43].

In addition, the pharmaceutical industry produces dosage forms for inhalation, when using which there is automatic coordination of acts of inhalation and drug administration, which is very important in children's practice; delivery of active substances to the lungs is carried out using inhalation devices, such as nebulizers, aerosolizers, spinhalers, turbohalers, etc. [2, 17-19].

Based on the thesis regarding the acceptable taste properties of the dosage form as one of the key criteria that allow the use of the drug in pediatrics, as well as the results of research that indicate the possibility of developing medicinal products based on confectionery products, the creation and introduction of medicinal caramels into medical practice is quite promising, marmalade, jelly. [20; 50-53].

Thus, among the factors that determine the degree and nature of the effect of pharmacologically active substances on the child's body, the key place is occupied by the type of dosage form, which largely affects the bioavailability of the drug due to the variation in the level and intensity of the processes of absorption, binding to blood proteins, distribution and elimination [67]. The peculiarities of the market segment determine a fairly high level of requirements for pediatric drugs, which primarily include high bioavailability with an optimally expressed pharmacotherapeutic effect, the use of only high-quality substances and an adequate selection of excipients according to age. At the same time, the effect of the medicinal product should be manifested against the background of the minimal risk of developing adverse reactions. In the light of these considerations, the organoleptic aspects of the use of the drug (pleasant taste, smell, attractive appearance) are also of particular importance.

It is important to emphasize the requirement for the absence of active substances that affect the growth and development of tissues, reduce immunity or are toxic. As excipients for children's dosage forms, only indifferent, natural products that are approved for use in medical practice can be used. Based on this, it is not recommended to add sugar and ethanol to the drug. In this regard, attention is drawn to the principled position of pharmaceutical companies of a number of countries (Great Britain, Denmark, Austria, etc.), which produce medicinal products for pediatric practice without the content of ethanol, the lethal dose of which at a concentration of 95% for young children is only 10 ml (tabl. 1.2).

Table 1.2

Analysis of maximum permissible concentrations of ethanol in drugs for pediatrics

Age of the child	**Ethanol concentration, %**
under 6 years old	0,5
ages 6–12	5
over 12 years old	10

Given the rather high risk of drug overdose in children, requirements have been established regarding the presence of a dosing device in reusable drugs (aerosols, syrups, suspensions, etc.) and the impossibility of independent use of drugs by children (especially in the case of containing potent substances) [22, 74-76].

Recently, interest in the aspect of bacteriological purity of medicinal forms, including those intended for newborns and infants, has increased significantly. It is important to note that the danger of microbial contamination is due to both the

possible pyrogenic reaction and the probable modification of the medicinal substance into a toxic product.

Medicinal forms for newborns and liquid medicines intended for children of the first year of life must be sterile (or prepared in aseptic conditions). In this aspect, soft medicinal forms, as well as syrups, mixtures, which have a high concentration of carbohydrates and / or contain extracts from medicinal plant raw materials and are a good substrate for the development of microorganisms [72, 78], are particularly dangerous.

So, as an interim summary, we can come to the conclusion that the dosage forms in which drugs for pediatric practice are produced today are quite diverse, which, in turn, allows for highly effective and safe pharmacological correction of pathological conditions of various genesis. However, in practice, it is quite difficult to carry out rational pharmacotherapy: the saturation of the pharmaceutical market with drugs with children's dosages and forms of release convenient for use in pediatrics is insufficient. Despite the fact that the range of children's medicinal forms has expanded over the past decades, less than 50% of drugs have established effectiveness and safety in children, which, in turn, leads to irrational (off label, unlicensed drug) prescribing and provides quite high indicators (up to 10 %) of hospitalization as a result of drug complications [65, 68, 71-72].

CONCLUSIONS TO CHAPTER I

1. It has been established that during the pharmaceutical development of drugs in pediatric practice, it is necessary to take into account the peculiarities of the pharmacodynamics and pharmacokinetics of the active substance in children of different age groups, as well as the possibility of side effects of the latter. It is quite significant to correct the doses of drugs taking into account the peculiarities of the ontogenetic development of the child, anatomical and physiological features, as well as the nature and degree of severity of the pathological process.

2. It has been established that the problem of polypharmacy is particularly relevant in pediatrics: the risk of complications increases when several drugs are prescribed at the same time against the background of physiologically determined slowed metabolism. So, to date, it has been established that in the case of combined therapy with antibiotics, antipyretics, antihistamines and immunostimulatory against the background of viral diseases, the percentage of allergy is much higher than with the separate use of chemotherapeutic agents in the treatment of bacterial infections.

3. The pharmaceutical forms in which drugs for pediatric practice are produced today are quite diverse, but in practice it is quite difficult to carry out rational pharmacotherapy: the saturation of the pharmaceutical market with drugs with children's dosages and forms of release convenient for use in pediatrics is insufficient.

4. It was established that less than 50% of drugs have established effectiveness and safety for children, which, in turn, leads to irrational (off label, unlicensed drug) prescriptions and ensures fairly high rates (up to 10%) of hospitalization as a result of drug complications.

CHAPTER 2. STUDY OF REGULATORY POLICY IN THE DEVELOPMENT OF CHILDREN'S DRUGS.

2.1 Regulatory aspects of pharmaceutical development of drugs for children.

For pediatric medicines, legislation came into force throughout the EU in January 2007 [35]. This law aims to improve the safety of drugs for children by expanding research, development and registration of drugs based on specific pediatric experience, without subjecting the pediatric population to unnecessary clinical trials. Legislation establishes requirements for the pharmaceutical industry in relation to the development of drugs for pediatric use. A framework for administering the operation of the legislation is also being considered, including the establishment of a pediatric committee.

The EU has issued guidance regarding the above legislation. This guidance concerns the conduct of pharmacovigilance of medicinal products used in pediatrics and is intended for both the pharmaceutical industry and national authorities (fig.2.1).

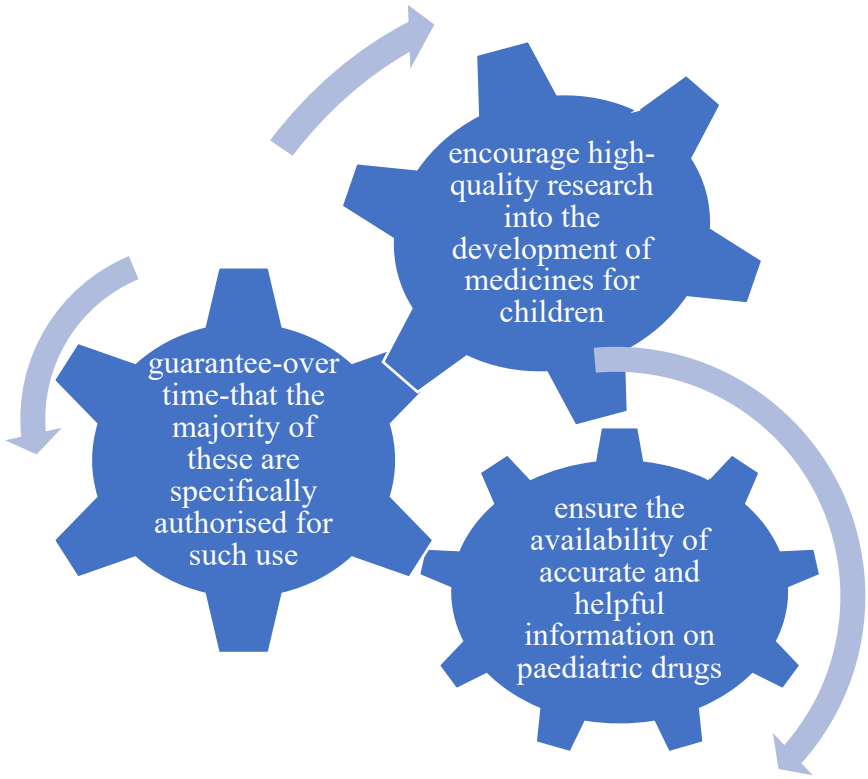

Fig.2.1. The regulation aims.

According Article 1 of Directive 2001/83/EC, the following definitions shall apply:

1) ‘paediatric population’ means that part of the population aged between birth and 18 years;

2) ‘paediatric investigation plan’ means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population;

3) ‘medicinal product authorised for a paediatric indication’ means a medicinal product which is authorised for use in part or all of the paediatric population and in respect of which the details of the authorised indication are specified in the summary of the product characteristics drawn up in accordance with Article 11 of Directive 2001/83/EC;

4) ‘paediatric use marketing authorisation’ means a marketing authorisation granted in respect of a medicinal product for human use which is not protected by a supplementary protection certificate under Regulation (EEC) No 1768/92 or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.

The analysis of the basic principles of pharmaceutical development and regulation of the circulation of drugs for pediatrics in the context of the international market showed that there is no single approach in global practice, however, pharmaceutical manufacturers of a number of countries are motivated to conduct well-planned, properly organized, ethically justified clinical studies with the participation of children. Thus, the regulatory policy in the USA is based on providing various preferences to the developers of children's drugs, as well as the mandatory nature of pediatric research (tabl.2.1) [10, 37].

Table 2.1

Key stages of the formation of regulatory policy in the context of the development of children's medicines in the USA.

1994	**Pediatric Labeling Rule**
	An attempt to improve existing instructions for the use of drugs by obliging manufacturers to review existing instructions for these use in children and submit appropriate amendments (Kessler's Pediatric Rule).
1997	**Pediatric Rule FDAMA** **Food and Drug Administration Modernization Act**
	Adoption of the Law on Modernization and Responsibility of the Federal Food and Drug Administration [providing the possibility of a 6-month extension of data exclusivity as an award to the manufacturer for conducting children's clinical trials and developing pediatric dosage forms ("pediatric exclusivity")].
2002	**BPCA: Best Pharmaceutical for Children Act**
	The law extends the program for encouraging children's clinical trials for another 5 years, and also establishes a mechanism by which children's clinical trials can be conducted.
2003	**PREA: Pediatric Research Equity Act**
	According to the PREA, manufacturers are obliged to submit data from children's clinical trials for all new medicinal products, new indications, new dosages, dosing regimens and routes of administration, while the application for registration must contain data to assess the safety and efficacy of medicinal products and justify the dosing regimen and route of administration for each pediatric categories of patients. Data from efficacy in adult clinical trials may be extrapolated if such extrapolation was supported by appropriate paediatric pharmacokinetics, pharmacodynamics, and safety studies. In certain cases, the manufacturer could receive a full or partial waiver of this requirement or a postponement of children's clinical trials.
2007	**FDAAA: Food and Drug Administration Amendments Act (Law on Amendments by the Food and Drug Administration)**
	Withacon, the FDAA extends two basic laws: BPCA i PREA.

The key vector in the pharmaceutical development of drugs for European pediatrics is directed towards the regulation of the procedure for conducting clinical trials (tabl.2.2-2.3).

Table 2.2.

Key stages of the formation of regulatory policy in terms of the development of children's medicinal products in Europe.

1997	**EMEA Round Table**
	The European Commission of the European Medicines Agency (EMEA) organised a round table of experts to discuss the problems of children's medicines. One of the recommendations of the round table was the awareness of the need to strengthen legislation, especially through the introduction of a system of economic incentives, to conduct children's clinical trials.
1998	**ICH Discussion**
	The European Commission initiated an international discussion of the problems of children's clinical trials within the framework of the International Conference on Harmonization of Technical Requirements for the Registration of Medicinal Products Intended for Humans. This international organization is working to harmonize the regulatory requirements of the European Union, the USA and Japan regarding the registration of medicinal products.
2000	**Guideline ICH E11** ICH E11 Guidelines for Clinical Studies of Medicinal Products in Pediatric Populations.
	The ICH E11 manual addressed the following aspects of pediatric clinical research: factors influencing the content of the research program; types of clinical trials; ethical issues in pediatric research.
2002	**Consultation Paper**
	Publication by the European Commission for discussion of the document "Best medicines for children – proposal for legislative action on paediatric medicines".
2006	**Pediatric Regulation Agreed**
	Approval of the document "Best medicines for children - proposal for legislative action on pediatric drugs".
2007	**Pediatric Regulation into Force**
	Entry into force of the document "Best medicines for children - proposal for legislative action on pediatric drugs".

In 2002, the Best Pharmaceuticals for Children Act (BPCA) was signed into law, providing an incentive of six months of marketing exclusivity for products studied in response to a written request for paediatric studies from the United States Food and Drug Administration [46]. The BPCA required a special safety review for adverse events reported for the year after a product has received its paediatric exclusivity. The adverse event reports are to be referred to the newly mandated Office of Pediatric Therapeutics (OPT), at which time the OPT can provide the report for review and recommendation by the Pediatrics Advisory Committee.

Since 2002, the US FDA has conducted postmarketing reviews of adverse events for 65 drug products studied under BPCA. Safety concerns warranting new labelling or further study were expressed for some products. The adverse events reported in connection with these products included deaths and serious events associated with the inappropriate use of opioid transdermal system medicines; neonatal syndrome with the ingestion of selective serotonin reuptake inhibitor. These reviews are in addition to the routine pharmacovigilance activities for all products in all populations and have helped to focus on safety issues that may present in paediatric patients.

In Canada, paediatric associations take the initiative to report ADRs resulting from the use of off-label products, in order to make data on medicine safety in 2 children available. These data are also shared with the national center.

It should be noted that a pediatric cluster was formed in 2007, which is an ethical and scientific basis for planning and conducting pediatric research. At the same time, during the period from 2007 to 2016, 129 discussions of relevant aspects of the development of children's dosage forms took place within the cluster, as well as an exchange of information on 400 objects [10, 37]. At the same time, it should be noted that only a combination of clinical studies in the pediatric population with an effectively functioning pharmacovigilance system in the country can serve as a guarantee of a complete understanding of the safety profile of pharmaceuticals in children.

Table 2.3.

Comparative analysis of regulatory policy in terms of the development of children's medicines in the EU and the USA.

Stage name	EU	USA
Regulatory authority	The European Agency for the Evaluation of Medicinal Products	Food and Drug Administration
Committee on Children	Paediatric Committee	Pediatric Review Committee
Enactment	2007	2007
Pediatric legislation	European Pediatric Regulation	BPCA, PREA
Main document	Paediatric research plan	Written request FDA
Application area	Medicinal and immunobiological preparations	Medicines
Initiator of the pediatric plan	Development company	Requirements FDA
Non-clinical studies	Must be included	Can be included
Characteristics of the drug	Full description of the product, including a description of dosage forms for different age groups	Declaration on the development of dosage forms for different age groups

In Japan, since 2000, the clinical research guidelines "Guidelines for the Development of Medicinal Products for Pediatric Use" and "General Provisions for Clinical Research of New Medicinal Products" have today been replaced by the requirements of ICH E11.

It should be emphasized that when data from clinical studies in pediatrics are provided, the term of drug registration can be extended up to 10 years [23-36; 37].

Thus, summarizing all of the above, it should be noted that the principles of rational pharmacotherapy in pediatric practice should be built exclusively taking into account the characteristics of the child's body, which will greatly limit the possibility of developing direct adverse reactions and allow for the most effective and safe treatment.

The solution to the problem of rational pharmacological correction of children's diseases is aimed at taking into account both medical and biopharmaceutical aspects, including taking into account the latest achievements of pharmaceutical technology, which, in turn, will ensure the stimulation of production on the domestic pharmaceutical market of a wide range of dosage forms that will meet acceptable for pediatrics to therapeutic concepts [82-84]. At the same time, models of state regulation of the circulation of drugs for children require a balanced and scientifically based approach.

2.2 . Principles of creation and expansion of the National List of Essential Medicines.

Nonavailability of child-size medicines encourages the use of adult dosage forms, splitting them into parts before giving them to a child. This practice is not scientific and is far from rational since children are not just miniature adults. Their anatomical and physiological characteristics are very different from those of adults. To extremely avoiding the risks of medicines, use in children, medicines used by children should suit a children’s size, age, physiologic condition, and treatment requirements. To satisfy children’s basic medicine needs, WHO has published seven editions of the WHO Model List of Essential Medicines for Children (EMLc) from October 2007 to July 2019. Besides, in 2009, the WHO launched the “Better Medicines for Children” initiative and “Make Medicines Child Size” campaign to enhance the accessibility of safe, effective, and quality medicines for children by promoting awareness and action through research, regulatory measures, and policy changes.

So far, a large number of researchers around the world have conducted a series of studies to evaluate the accessibility of medicines, and most of the studies have adapted the WHO standardized methodology. According to the data recorded by the WHO website, as of 2019, 76 studies from 55 countries world-wide have been conveyed by using the WHO standardized methodology. Among them, seven studies have evaluated the accessibility of medicines on essential medicines for children, and the results demonstrated that the overall availability of medicines for children was low.

Essential medicines are those that satisfy the priority healthcare needs of the population. They are selected on the basis of disease prevalence, evidence on efficacy, safety and comparative cost- effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford. The purpose of the original WHO proposal for the programme of essential medicine was developed in 1975 based on the experience of some countries, like Sri Lanka, where programmes of basic or essential medicines had been implemented. The objective was to make the most necessary medicines available to populations whose basic health needs could not be met by the existing supply system.

An international Expert Committee was appointed by WHO to recommend how a national essential medicines programme could be implemented. The Expert Committee issued its report in 1977.

The report included the selection criteria for an essential medicine (tabl.2.4) and also the first WHO Model List of Essential Medicines (EML) of 208 medicines. Since then the List is updated every 2 years. Its content and the process by which it is updated are intended to be a model for developing countries.

Table 2.4

The criteria for determining if a medicine is essential.

	CRITERIA
I.	Having adequate evidence of efficacy and safety from clinical studies in a variety of medical settings.
II.	Availability in a form that is made properly with adequate bioavailability and stability under anticipated storage conditions.
III.	The use of the medicine for its indicated purpose has been well established.

The essential medicines concept of purchasing a limited list of essential medicines for a health service and making them available has been widely accepted. Many United Nations agencies, including UNICEF and United Nations Refugee Agency, major non-governmental organisations and international non-profit supply agencies limit the medicines they purchase for donations to those on the EML.

The Model List is drawn up by the WHO Expert Committee on the Selection and Use of Essential Medicines usually convened every 2 years. The Committee comprises 8–12 members drawn from the WHO Expert Advisory Panels based on equit- able geographical representation, gender balance and professional competencies in order to provide a representation of different approaches and prac- tical experience from all regions of the world. Members of Expert Advisory Panels are proposed by WHO and, when approved by their respective government, appointed for one or more periods of up to 4 years. Meetings of the Expert Committee are closed. Observers may be invited in accordance with WHO Regulations to attend all or parts of the meetings of the Expert Committee.

The WHO EML is a model and is to be adapted to the local environment and needs at national levels. National lists of essential medicines provide a public health basis for focus and expenditure in the pharmaceutical sector. They are used to guide

the procurement and supply of medicines in the public sector, reimbursement schemes, medicine donations and local medicine production.

Of the 151 countries surveyed in 2007 by WHO 131 had an essential medicines list. Most developing countries have national lists and some have provincial or state lists as well. However, revisions of the list did not take place regularly until recently. The 22nd WHO Model List of Essential Medicines and the 8th WHO Model List of Essential Medicines for Children were approved by the 21st WHO Expert Committee on the Selection and Use of Essential Medicines in 2021.

In the new WHO list, as a result of the changes, the total number of medicinal products in the List of medicines is 479 (of which 365 INNs belong to the main list, and 114 INNs belong to the additional list). The total number of listed drugs takes into account additions and exceptions (fig. 2.2).

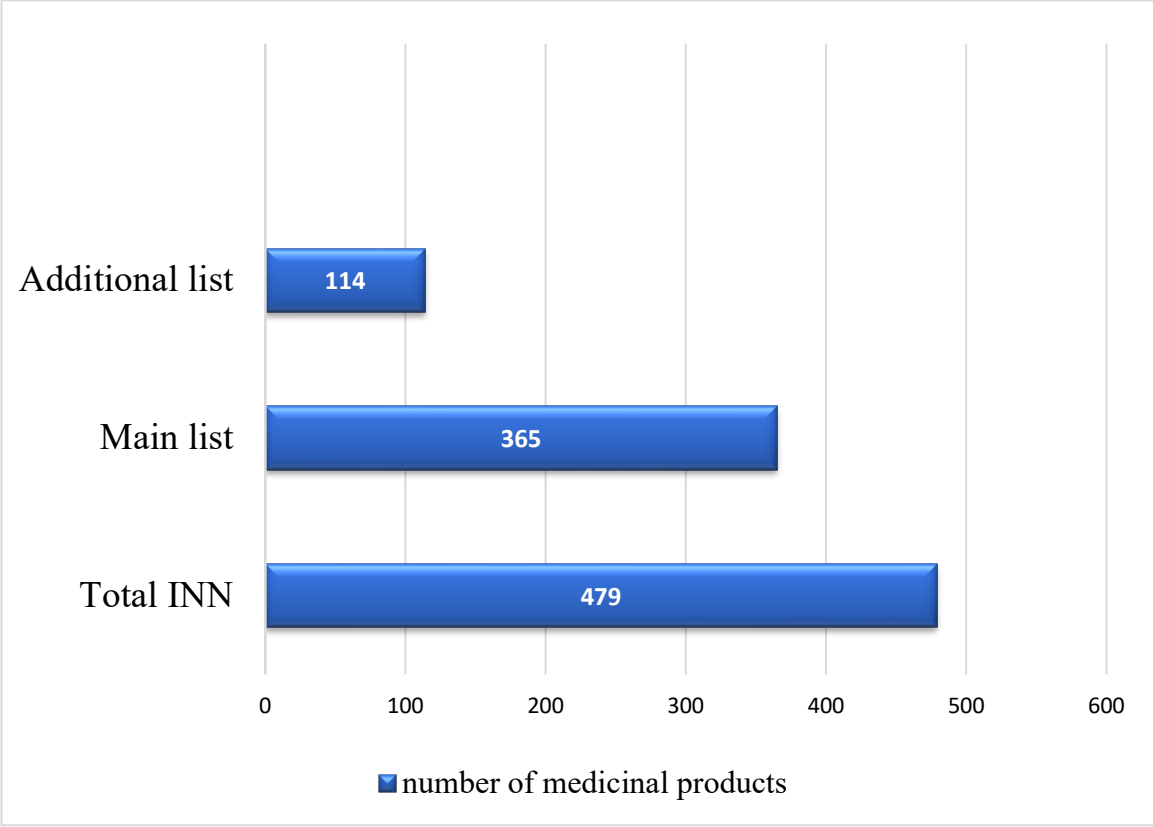

Fig. 2.2 Composition of the WHO list by INN.

The basic list of essential medicinal products recommended by WHO has a recommendation function and is not used for the purposes of price regulation of medicines.

2.3 The WHO National List of Essential Medicines for Children and the British National Formulary for Children as a basis for providing rational pharmaceutical care to children.

The WHO National list has been updated every two years since 1977, but it was not until 2007 that a separate EML was created for children under 12.

The first Expert Committee responsible for developing the first EML had eight members, and four temporary advisers, none of them a paediatrician. The report mentioned children only once, in the description of the Model drug information sheet (Dosage regimen: Average and range for adults and children). Although the EML included some paediatric medicines, children's medicines were not systematically considered during the first 30years of the EML, and the Expert Committee included a paediatrician only three times, in 2003, in 2005 and two in 2007. In 2006 WHO together with UNICEF organised an expert consultation to consider ways of tackling the problem of lack of essential medicines for children.

Since then, the EMLc has been revised seven times and the current version is the eighth. The Pediatrics Subcommittee of the Expert Committee developed the first two EMLs for children. The third was developed by an Expert Committee with a balanced experience of adults and children.

In 2021, the 8th list of EML for children was released, which includes 350 items of EML, for comparison, the 1st list consisted of only 264 drugs.

The main list of medicines for children is a list of the minimum requirements for medicines of the basic health care system. The list includes the most effective, safe and cost-effective medicinal products intended for priority conditions. Priority conditions are selected based on their current and statistically estimated future public health importance and cost-effectiveness of treatment.

Also, an additional list is added to the main list, which is a list intended for priority diseases, for the treatment of which specialized institutions for diagnostics and medical assistance are needed. Also, the lists indicate that, in case of doubt, drugs can be classified as additional on the basis of consistently high cost or lower cost-effectiveness in different institutions.

According to the analysis of 8 of the lists of Essential Medicines (EM) for children under 12 years of age, it was established that the main part of the drugs is presented in liquid forms of release, namely solutions [40-44; 46].

The importance of providing pharmaceutical care to children is also confirmed by the WHO document "Investing in the Future of Children: European Strategy for the Health of Children and Adolescents, 2015-2020". The goal of the document is to ensure a healthy lifestyle and promote well-being for all at all ages, according to which countries should ensure access to safe, effective, high-quality and affordable essential medicines based on a strong and effective health care system [2; 44].

The lack of children's medicinal forms is associated with many factors, but one of the main ones is the insufficient number of clinical studies with the participation of children, which is due to the difficulty of conducting them for drug developers, ethical problems, difficulties in obtaining informed consent from parents, etc. [9, 10].

The lack of registered children's dosage forms leads to the prescription of medicines "off-label" ("outside the instructions"), in violation of the prescriptions of the approved instructions, and this situation is characteristic of pediatric practice in many countries. Most often, these disorders occur in the age group of children under two years of age [11, 12].

Prior to the creation of the WHO National Formulary for Children, the first British National Formulary for Children (BNFC) was issued in 2005 at the initiative of the National Institute for Clinical Excellence (NICE), which contained data on more than 600 medicines. The following organizations participate in the preparation of the BNFD: the British Medical Association, the Royal Society of Pharmacists, the Royal University of Pediatrics and Child Health, and the Pharmaceutical Group for Neonatology and Pediatrics [8].

The main tasks of BNFC, which are aimed at ensuring rational pharmacotherapy, are presented in figure 2.3.

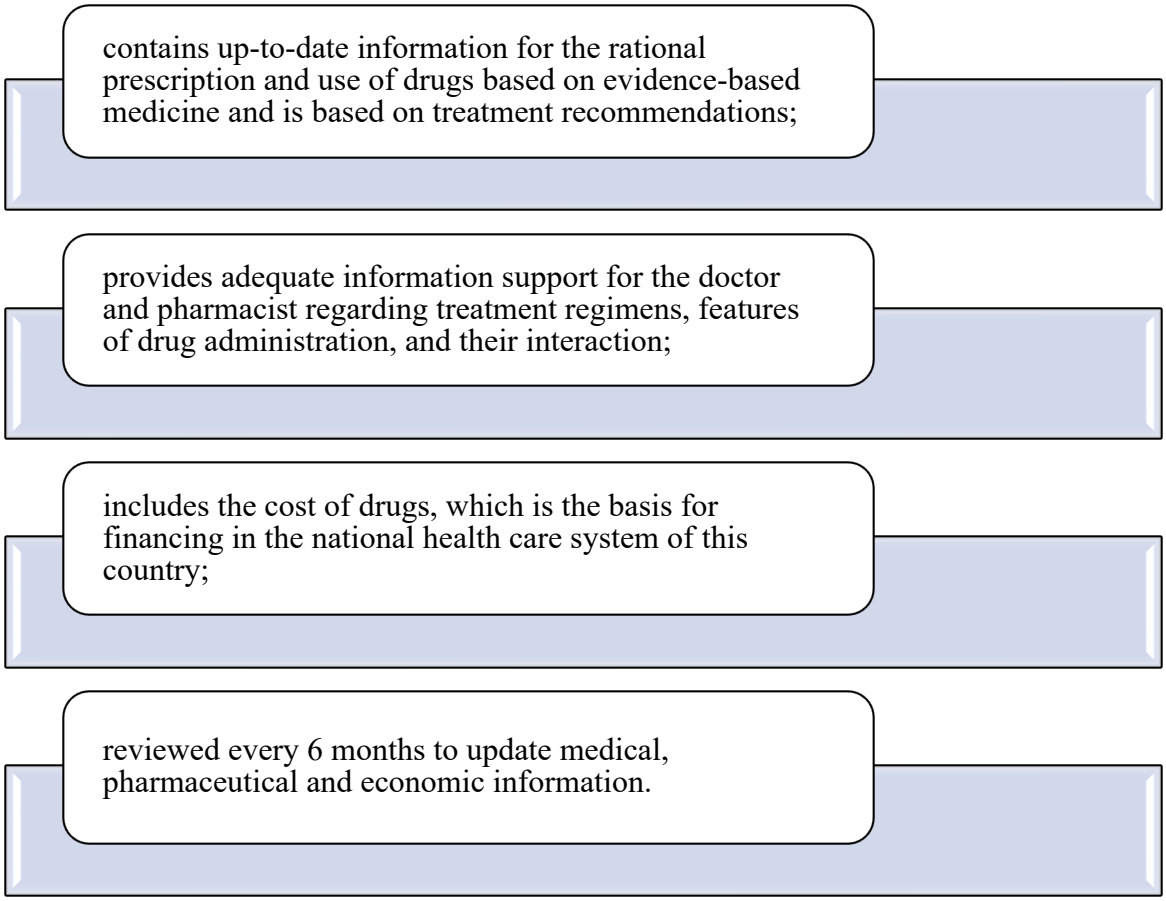

Fig. 2.3 Analysis of the main tasks of the BNFC.

On the first pages of each new edition of the BNFC, all changes compared to previous editions are listed, for example, 52 changes were made in the 2006 edition, which relate to individual provisions of articles on clinical symptoms, treatment regimens, and aspects of drug use. In the BNFC, the main clinical symptoms of gastroesophageal reflux, its manifestations in children and the main treatment schemes are given for the first time; the symptoms of Kawasaki syndrome when using acetylsalicylic acid are described, drugs are indicated for the treatment of epileptic status, for the regulation of lipid levels, etc. [8; 87-89].

It should be noted that the BNFC contains clear information about the use of drugs in children, concisely represented by section.

Sections are given in table 2.5.

Table 2.5

Analysis of BNFC sections

Sections	**Content**
I.	Indications, including data on aspects of monitoring in liver, renal disorders, pregnancy, breastfeeding.
II.	Contraindications to use (specific diseases are clearly indicated, in contrast to the common formulation – "hypersensitivity to drugs").
III.	Contraindications to the drug: most often observed and serious.
IV.	Licensed use: registration of the drug.
V.	Use and dose, frequency of administration for children of all age groups.
VI.	International non-proprietary name of the drug, indicating the dosage form, color, coating, active and auxiliary substances in the dosage form.
VII.	Generic names of drugs indicating the sugar-free dosage form (for diabetics), as well as active ingredients and their quantity (mg/ml).
VIII.	The base cost of the drug, depending on the dosage form, expressed in pounds sterling.

Adopting the information system regarding drugs that are discarded by the BNFC will allow the creation of a domestic formulary based on the best European model, which in turn will significantly improve the quality of pharmacotherapy in pediatric practice.

All drugs included in the BNFC are classified into 15 groups, depending on the systemic pharmacotherapeutic action or impact on systems/organs (fig. 2.4).

Appendices contain differentiated information about drugs (in particular, drug interactions), as well as available applications for nurses and dentists, which include a list of drugs approved for prescription [40, 44; 55].

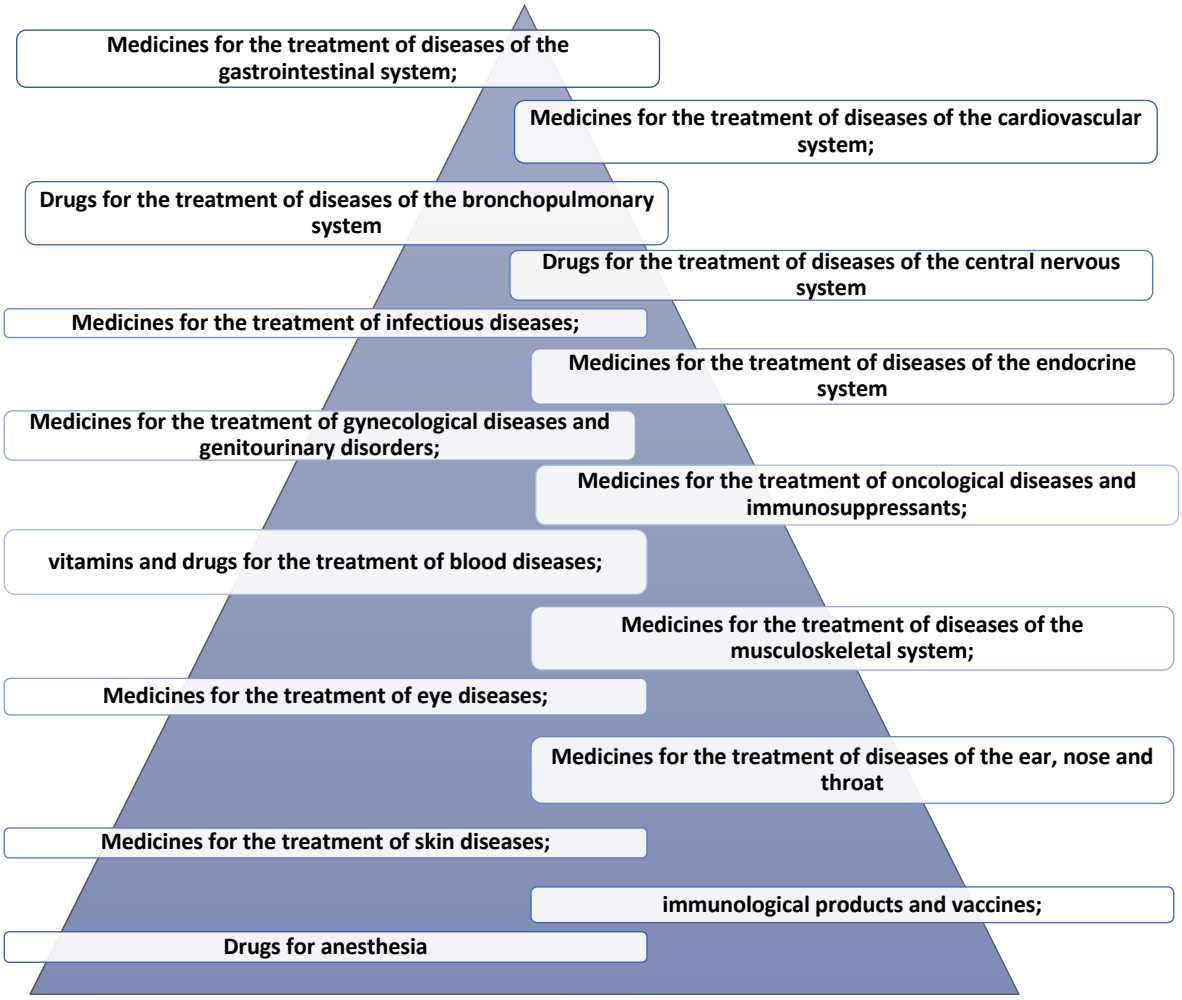

Fig. 2.3 Groups of drugs included in the BNFC.

Summarizing, it should be noted that the BNFC contains information on the provision of care in emergency situations in children with a clear algorithm for the administration and dosage of drugs, while these drugs have proven effectiveness and safety. In this formulary, all information about drugs is clearly structured and contains both classical and specific data, in particular, contraindications to use, doses depending on the age and body weight of the child, the composition of the dosage form with an indication of active and auxiliary substances with an emphasis on the presence of sugar in the drug, all possible drug interactions with other groups of drugs and individual drugs. The formulary also provides information on the schemes for the prevention of children's diseases and treatment for emergency conditions with gradation of doses depending on the age of the child [12-18, 25].

CONCLUSIONS TO CHAPTER II

1. It has been established that the regulatory policy in the USA is based on the provision of various preferences to the developers of children's drugs, as well as the mandatory nature of pediatric research. The key vector in the pharmaceutical development of drugs for European pediatrics is aimed at regulating the procedure for conducting clinical trials.

2. It has been established that the problem of polypharmacy is particularly relevant in pediatrics: the risk of complications increases when several drugs are prescribed at the same time against the background of a physiologically determined slowed metabolism.

3. The principles of rational pharmacotherapy in pediatric practice should be built exclusively taking into account the characteristics of the child's body, which will greatly limit the possibility of developing direct adverse reactions and allow for the most effective and safe treatment.

4. Problems of rational pharmacological treatment of children's diseases should be solved taking into account both medical and biopharmaceutical aspects. At the same time, models of state regulation of the circulation of drugs for children require a balanced and scientifically based approach.

5. WHO's national list of EM has been updated every two years since 1977, but in 2007 a separate list of EM for children under 12 was created. In 2019, the 8th list of EML for children was released, which includes 350 items of EML, for comparison, the 1st list consisted of only 264 drugs.

6. It has been established that the BNFC contains information on the provision of assistance in emergency situations in children with a clear algorithm for the administration and dosage of drugs, while all the listed drugs have proven effectiveness and safety.

CHAPTER 3. STUDY OF MODERN APPROACHES TO THE FORMATION OF REGULATORY LISTS FOR PROVIDING PHARMACEUTICAL AID TO CHILDREN.

3.1 Studies on the selection of essential medicines for inclusion in the National List of Tanzania.

According to the State Statistics Service, in the period 2012 - 2025, there was a significant increase in the child population, aged 0 to 15, in Tanzania. Currently, Tanzania's population is very youthful. Children below 15 years comprise about 44% of the population and an additional 19% are youth between 15-24 years [41]. The number of children has increased, and the number of primary diseases has decreased. Positive changes in the primary morbidity are caused to a greater extent by the increase in the total number of children, and not by the reduction in the number of cases of newly registered diseases, the number of which increased during this period. According to the Institute for Health Metrics and Evaluation, HIV/AIDS is the leading cause of death in Tanzania not only for adults but for children, followed by lower respiratory tract infections and diarrheal diseases [44]. Nearly 90 percent of HIV-positive children worldwide and roughly two-thirds of all HIV-positive people live in sub-Saharan Africa. Most of the massive efforts to roll out antiretroviral drugs has concentrated on adults, not children. Children in Africa continue to die of AIDS at high rates. If untreated, AIDS kills 50 percent of children born with HIV before their second birthday [51]. Largely preventable and treatable diseases such as malaria, pneumonia and diarrhea cause the death of 270 children under 5 years of age every day. In Tanzania, diarrhea is estimated to account for around 5 percent of child deaths.

The overall health situation has improved for Tanzanian children in the last two decades, and quite dramatically in recent years. There are wide socio-economic and geographical disparities in child mortality, largely due to inequities in access to, and use of, health services. Regional and economic inequities cause imbalances in child survival. The general trends in the health of the children's population confirm the need to improve the quality of medical care for children, one of the mechanisms

of which is the improvement of pharmaceutical care and the expansion of the range of domestic children's medicines.

Tanzania has a National Drug Policy, defined by law, which includes a national list of essential medicines, as a tool for its implementation [30]. This tool is a general list that guides the availability of medicines in the health care system throughout the country. In the latest versions, the list gradually includes medicines and dosage forms for pediatrics. However, recent studies show a lack of access to age-appropriate drugs in government facilities, as well as a lack of some essential drugs in the Tanzanian pharmaceutical market [32].

The Tanzania Medicines and Medical Devices Authority (TMDA) is mandated by the Medicines and Medical Devices Act (Cap 219) to regulate the manufacturing, importation, distribution and sale of medicines, medical devices and diagnostics [10]. As the first African regulatory authority, TMDA was assessed by the WHO in 2018 as a well-functioning regulatory system for medicinal products [11]. Tanzania established its first NEML in 1991 and has had five updates, the latest is 2021. Medicines are supplied through the government's Medical Stores Department (MSD) and private organizations. The MSD is the main procurer of EMs in the country and provides medicines to the public sector and other organizations involved in healthcare provision. Tanzania’s pharmaceutical market was worth an estimated $400 million in 2015 and locally produced products constituted 12% of the overall market in 2014 [11]. Local manufacturers engage only in secondary and tertiary manufacturing [10], raw materials are imported mainly from India [13].

The purpose of our study is to compare the sixth edition of the National Essential Medicines List in Tanzania (NEMLIT) 2021 with LEMC 2021, identifying the lack of medicines and medicines for children in the Tanzanian reference list, in order to identify the need for special government policies to stimulate this area.

We identified EMs by comparing INNs with those on the NEML. The Tanzanian NDR lists products by manufacturer and country. We analyzed the number of local drug manufacturers, the number of registered local products, and the market status of these products in emerging markets for Tanzania [44].

Table 3.1 shows that 4 companies were registered as local drug manufacturers in Tanzania with 97 registered products. Some emerging markets have one or more locally produced products. Tanzania had 39 EM products made in the country. These products corresponded to 24 (5%) of the individual drugs listed in the NEML for Tanzania [51].

Table 3.1

Number of local manufacturers n, registered products and number and proportion of locally produced EMs in Tanzania n, (%)

Content	**Number**
Local manufacturers of medicines	4
Locally produced Medicine products	97
NEML products	39 (40%)
Medicines on NEML	510
Locally produced EMs	24 (5%)

Using 2021 NDRs for country, we analysed the number of EMs in each therapeutic class, by registration status and whether produced locally (table.3.2).

The Tanzanian NEML has 28 therapeutic classes. The number and proportion of EMs that were registered were 269 (53%) in Tanzania. Tanzania had 24 locally produced EMs across 11 drug classes, with no locally produced EMs for 16 classes. Of the 28 classes, seven classes (marked by an asterisk) had no local production in country. The anti-infective class had the highest number of locally produced EMs with 11 produced in Tanzania. The percentages of locally produced EMs varied across therapeutic classes with no local production for several classes.

Table 3.2

Number of EMs by therapeutic class, registration status, and proportion (%) produced locally from 2021 NDRs.

Therapeutic class	**Local EMs *n* (%)**	**EMs *n***	**Registered EMs *n* (%)**
Therapeutic classes common to the WHO National List with some locally produced essential medicines			
Anaesthetics	1(7)	35	11(30)
Medicines for pain and palliative care	2(9)	23	16(69)
Anti-allergics and medicines used in anaphylaxis	2(33)	6	6(100)
Antiepileptics/anticonvulsants	none	7	6(86)
Anti-infective medicines	11(11)	99	74(75)
Anti-migraine medicines	none	5	4(80)
Anti-parkinsonism medicines	none	4	1(25)
Anti-neoplastic and immunosuppressive	none	43	19(44)
Medicines affecting the blood	2(15)	13	6(46)
Cardiovascular medicines	1(3)	38	24(63)
Dermatological medicines (Topical)	4(20)	20	11(55)
Disinfectants and antiseptics	1(20)	5	1(20)
Diuretics	none	4	3(75)
Gastrointestinal medicines	5(50)	28	13(46)
Hormones, other endocrine medicines and contraceptives	2(9)	31	18(58)
Ophthalmological preparations	3(17)	46	18(39)
Peritoneal and haemodialysis solutions	n/a	none	n/a
Medicines for mental and behavioural disorders	none	25	13(52)
Medicines acting on the respiratory tract	1(14)	7	4(57)
Solutions correcting water, electrolyte and acid–base disturbances	none	7	5(71)
Vitamins and minerals	1(7)	14	2(14)

Table 3.2 continuation

Therapeutic classes common to WHO NML, without locally produced EMs			
*Antidotes and other substances used in poisoning	none	9	1(11)
*Blood products of human origin and plasma substitutes	none	7	none
*Diagnostic agents	none	2	2(100)
*Immunologicals and vaccines	none	16	1(6)
*Muscle relaxants (peripherally acting) and cholinesterase inhibitors	none	1	1(100)
*Oxytocics and anti-oxytocics	none	6	6(100)
*Ear, nose and throat medicines	none	7	3(37)
Therapeutic classes, only for Tanzania, without locally produced essential medicines			
Specific medicines for neonatal care	none	1	1(100)
Medicines for neurosurgical use	none	1	none

Priorities for local production should be determined by the country's National List of Essential Medicines - this is the main requirement of the WHO framework for local production [52]. In Tanzania, four local companies produced 5% of medicines on the NEML and two-fifths were EM products.

Local production of EMs is important in the context of recent health emergencies. The United Nations Conference on Trade and Development (UNCTAD) recognizes that the current COVID-19 pandemic exposes the vulnerability of drug supply chains that rely on a few manufacturers for raw materials or finished products [49]. Therefore, reducing reliance on imports is a key step in strengthening public health security. The NDL analysis highlights the importance of the country's presence of NEML and locally produced products to inform national pharmaceutical plans and strategies to increase the availability of EM for all segments of the population [21].

Our analyzes of individual medicines show that setting national priorities for essential medicines is a task that goes beyond updating the NEML, followed by

decision steps that are then applied to further reduce medicine choice. should be provided by the public health system [10,22]. These solutions operate differently depending on the medical groups and complicate the work in terms of health systems. We have summarized the results of our analysis in table 3.3.

Table 3.3

Thematic summary of findings regarding NEML updates in Tanzania

	Content	**Persons involved in the update and related implementation**	**New Lists and Availability of Priority Medicines**
National Essential Medicines List for Tanzania (NEMLIT) First published 1971a; Most recent: 2021 (6th edition)	Increased the total number of medicines to 583 Antibiotics classified as access, watch or reserve List indicates the level of healthcare level in which a particular medicine is to be found	• State and non-state, national and international actors; • Clearly prescribed roles under purview of Ministry of Health; • National medicines and therapeutics committees lead process; • Global stakeholders—WHO, iDSI, PRICELESS; PATH, Swiss Agency for Development and Cooperation and the Global Fund.	• Followed the WHO recommended process; • Over 10 meetings of the technical committees; • No challenge reaching consensus; • The latest list was updated concurrently with revision of standard treatment (clinical) guidelines; • HTA integrated in the process, which includes the use of cost- effectiveness findings; • Fragmentation of medicines funding; • The use of the list for procurement and clinical practice is widespread; • Cancer: Lacking reliable data on prevalence; • Hepatitis C: prevalence unknown, though to be high; • Tuberculosis: well-documented data on prevalence.

The new essential medicines list is now more prioritised than before in Tanzania. The process of updating NEMLs can be investigated from the perspective of the stages and interactions during each update, or more broadly, how the practice in each country has developed over time. The 1977, 1981 and 1986 lists were only

drug lists. The NEMLIT &STGs edition started in 1991, then 1997, 2001, 2007, 2013, 2017 and 2021.

Research in the qualification work shows that NEML updates follow a structured process aligned with WHO guidelines and are influenced by prioritization, procurement planning, and demand, funding and cost considerations. Analysis at the national policy level that NEML implementation should be the subject of increased attention and systematic review, since prioritization and accessibility are two sides of the same coin and benefit from the analysis as such.

3.2 Comparative analysis of drugs included in the List of drugs for children of WHO and the National List of Tanzania.

The List of Essential Medicines for Children is a model list that can be adapted by countries according to their needs and circumstances. It is a dynamic tool that is periodically reviewed and updated by ad hoc committees, as has been the case for the core Essential Medicines List for 50 years. LEMC, even in its seventh version (2021), remains incomplete and certainly unsatisfactory due to the world's lack of appropriate medicines for children. The essential medicines selection process is based on internationally recognized procedures based on an assessment of existing data on efficacy and safety of use, patient convenience, and cost-compatibility with patient or societal resources.

For pediatric medicines, this evaluation is limited by the scarcity of available evidence and of well-performed controlled clinical trials in children, by the limitations of the pharmacokinetic knowledge in different age groups, as well as by the scarcity of appropriate formulations for subgroups in different stages of physiological development, e.g. preterm neonates, full term neonates, infants and toddlers, and older children and adolescents.

In 2007, the WHO released the first edition of the Model List of Essential Medicines for Children, the seventh edition of which, supplemented by 25 medicines, was approved in March 2021 [5]. The British National Formulary for Children, which has existed for more than 30 years and is regularly revised and

updated in connection with the appearance of new FPs for children, has also found wide use around the world [6].

The updated WHO children's list includes 17 new drugs, as well as new indications for the use of 28 drugs. The changes recommended by the Expert Committee increase the number of medicines needed to meet the basic needs of the public health care, up to 350 (fig.3.1). Although this number may seem large, it is only a small fraction of those available on the market.

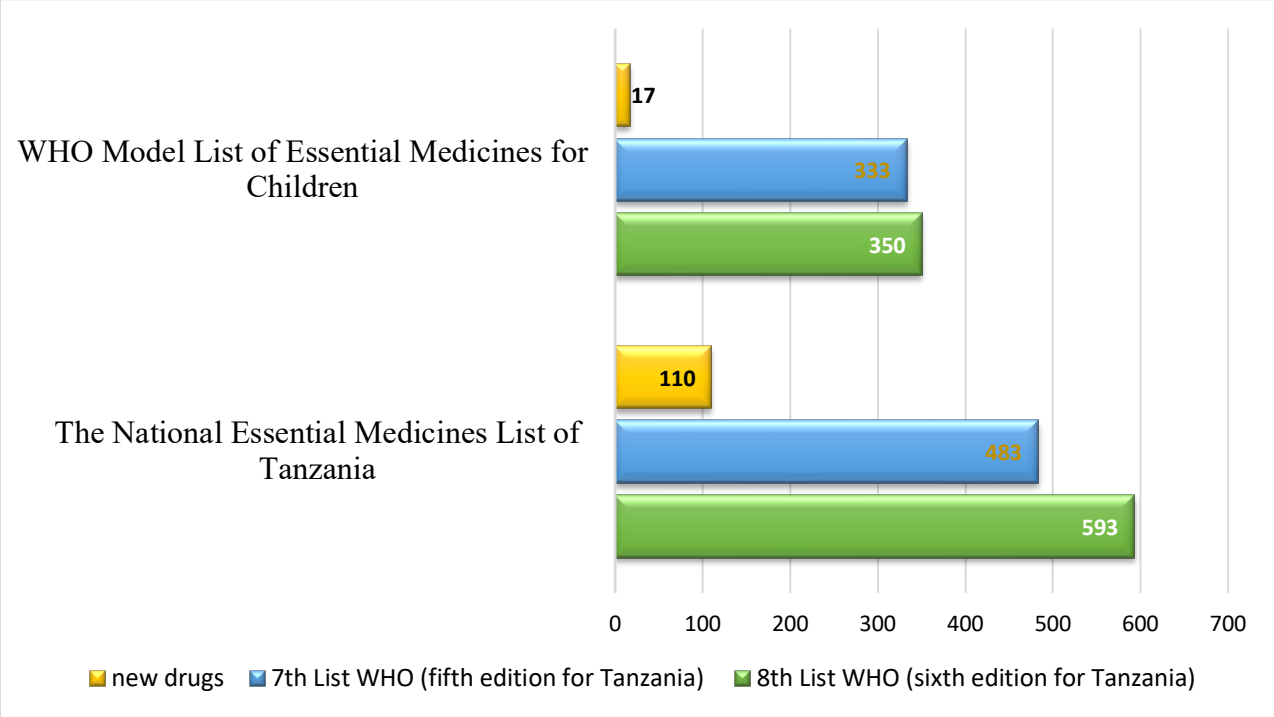

Fig.3.1 Analysis of WHO and Tanzania essential medicines lists.

The 6th edition of STG/NEDLIT addresses the challenges and gaps in health care delivery, in line with technological and medical advances. The new edition includes a number of significant improvements:

- Addition of 101 new drugs based on scientific evidence and clinical needs.
- Adopted the WHO classification of antibiotics into Access, Watch and Reserve groups to improve the use of antimicrobials and minimize the burden of antimicrobial resistance.
- New availability of medicines for noncommunicable diseases in primary health care settings.

- A new section on notifiable diseases has been added.

Tanzania has a national drug policy defined by law that includes the national list of essential medicines, as a tool for its implementation. This instrument is a general list that orients the availability of medicines in the health system nationwide. In the latest versions, NELT has progressively been including medicines and drug formulations for pediatric use. Nevertheless, recent studies demonstrate a lack of access to age-adapted formulations in public facilities, as well as the inexistence of some necessary formulations in the Tanzania pharmaceutical market.

Shortages of age-appropriate prescriptions for many pediatric medicines pose a serious challenge to pediatric therapeutic practice, adherence, and health care delivery worldwide. Participation of the state in increasing the availability and awareness of the treatment of the child population, is an important step towards achieving the Tanzanian government's goal of reducing child mortality by 80% by 2030. Key actions to date include ensuring an enabling policy environment; developing a holistic view of the pediatrics market that has been widely shared among partners to improve supply chain transparency; and testing the impact of ADD (Accredited Drug Dispensing) awareness efforts on improving knowledge, stocks, and dispensing behavior. Tanzania has made progress addressing child mortality through high coverage of childhood vaccinations, a strong malaria prevention and treatment program, and increasing awareness, prevention, and treatment of respiratory infections, diarrheal diseases, and under nutrition. The under-five mortality rate in Tanzania has decreased from 166 deaths in 1990 to 57 deaths per 1,000 live births in 2017.

Preventing under-five deaths remains a global priority and a major challenge for the Government of Tanzania. With a commitment to reduce child mortality by 80% by 2030, Tanzania has consistently focused on reducing childhood pneumonia, which is the leading cause of death on 15%. To achieve Tanzania’s childhood mortality targets, focused efforts are required within the public and private health care sectors, given the critical role they both play within the Tanzanian healthcare landscape. In 2021, the governments updated its clinical guidelines (i.e. Integrated

Management of Childhood Illness Guidelines, Standard Treatment Guidelines, and Pediatric Standard Treatment Guidelines) and National Essential Medicines List in the public sector market.

According to the register of medicinal products, as of September 1, 2021, the total assortment of children's medicinal products on the domestic pharmaceutical market was 22 INNs, presented in the form of 95 trade names of medicinal products and 248 medicinal products. These drugs, with the exception of homeopathic remedies, were divided into nine groups according to their ATC classification: A, B, C, H, J, L, M, N and R (fig.3.2).

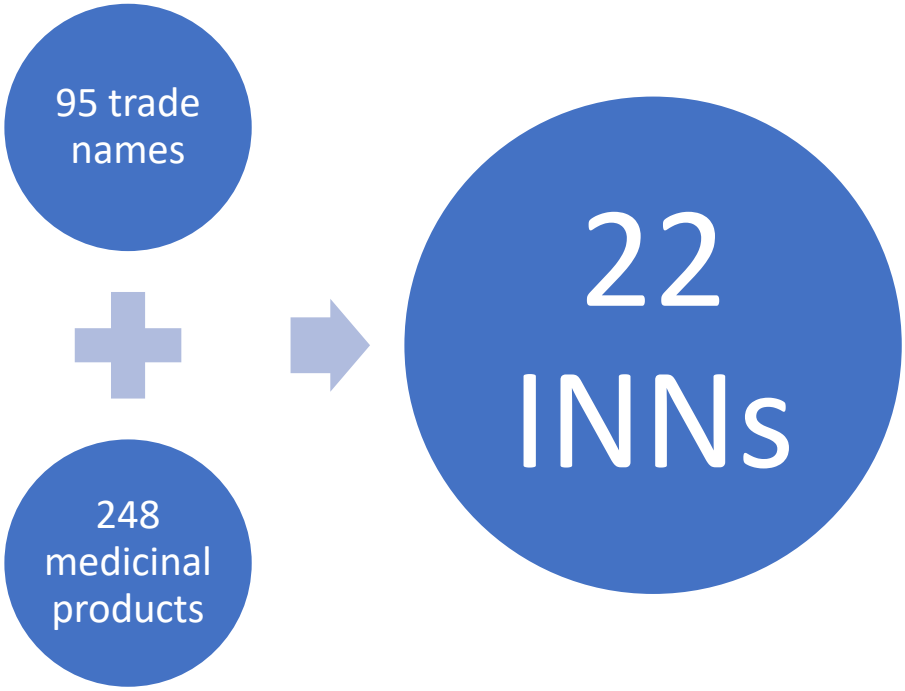

Fig.3.2 Total assortment of children's medicinal products.

It was established that the dominant share of children's medicines by the number of trade names (30.5%) and the number of drugs (39.1%) belongs to group A - drugs for the treatment of the digestive system and metabolism.

The intensity of acute respiratory distress syndrome in the first two years of a child's life averages from 4 to 9 episodes per year and is considered the maximum in the preschool period. Rhinitis is often the first symptom of ARI. Traditionally, the treatment of various forms of rhinitis in children of any age begins with the appointment of topical decongestants. The term "topical decongestants" combines drugs of different groups (sympathomimetics and selective α1-adrenomimetics).

The mechanism of action of all means of this group is the same - stimulation of α-adrenoblockers; when applied locally, they contribute to the reduction of swelling and hyperemia of the mucous membrane of the nose, reduce the amount of secreted secretion and facilitate nasal breathing [15].

A significant share in group R belongs to subgroup R05 - means used in case of coughs and colds, among which mucolytics can be distinguished (R05CB - 4.2%). Mucolytic therapy is widely used for acute and chronic respiratory diseases in children accompanied by mucositis and cough [16, 17].

In the course of the study, it was established that only 12 of the 22 INNs (monocomponent active substances) of the studied assortment of children's pharmaceuticals are represented in the regulatory lists (table 3.4). The largest number of INNs (10) in the assortment is included in the WHO List of Essential Medicines for Children (8th edition, 2021). Some INNs (azithromycin (J01FA), digoxin (C01AA), didanosine (J05AF), ibuprofen (M01AE), paracetamol (N02BE), phenobarbital (N03AA), valproic acid (N03AG)) are present in all lists.

Table 3.4

Analysis of the availability of children's medicines in regulatory documents

Regulatory lists		
List of drugs for children of WHO (8-th version, 2021)	National List of Tanzania (2021)	British National Formulary for Children (2019)
International non-proprietary names (INN)		
Macrogol	-	-
Azithromycin	Azithromycin	Azithromycin
Ibuprofen	Ibuprofen	Ibuprofen
Ketoprofen	-	Ketoprofen
Paracetamol	Paracetamol	Paracetamol
Phenobarbital	Phenobarbital	Phenobarbital
Valproic acid	Valproic acid	Valproic acid
Xylometazoline	Xylometazoline	-
Digoxin	-	Digoxin
Simethicone	-	Simethicone
Didanosine	-	Didanosine
Total 10 INN	Total 6 INN	Total 9 INN

The NEML retains its purpose of identifying medicines that are considered essential for the treatment of common disease conditions in Tanzania. A baseline survey of the pharmaceutical sector in Tanzania revealed that most of the drugs prescribed (98.5%) were included in the NEML [48].

The National Essential Medicines List (NEMLIT) presents essential medicines, for which health facilities at all levels requisite for management of priority diseases. The NEMLIT is based on the concept of essential medicines, defined by the WHO as those medicines that meet priority healthcare needs of the population and intended to be available within the context of functioning health systems at all times, with assured quality and at a price the individual and the community can afford. The concept emphasizes carefully and systematically selection of essential medicines using an evidence-based process with due consideration of clear evidence of safety and efficacy and comparative cost effectiveness.

The rationale for selecting a limited number of essential medicines is to enhance supply, improve rational use, and lower costs. Since the local health system dictates medicines supply to different levels of hospitals, a national committee also specifies in which levels of hospitals one particular essential medicine is expected to be available all the times. NEMLIT is used in relation to levels of care (fig.3.3). Medicines in the NEMLIT are grouped according to pharmacological groups and written alphabetically, in generic names, with their dosage forms and strengths.

levels of care	LEVEL OF MEDICINES USE
A	Medicines used at Dispensaries level
B	Medicines used at Health centers level
C	Medicines used at Council Hospital level
D	Medicines used at Regional Referral Hospitals
S	Medicines used at Zonal Referral, National and Special Hospitals

Fig.3.3 Level of medicines use.

Additionally, a new categorization of prescribing medicines with regards to expertise has been introduced to facilitate reimbursement of medicines by the NHIF. In summary, stocking and prescribing of medicines as per level of care will be: tertiary hospitals (A, B, C, D, S); Regional Referral Hospitals (A, B, C, D); District Hospitals (A, B, C); Health Centers (A, B) and dispensaries (A). Additional category reflects professional expertise; regardless of level of care: Specialists (A, B, C, D, S); Medical Officers (A, B, C, D); Assistant Medical Officer (A, B, C); Clinical Officers (A, B) and Assistant Clinical Officers (A) (tabl.3.5).

Table 3.5

Restrictions for Prescribing Medicines Listed in the NEMLIT

Level of Medicines with Regard to Service Provision		**Level of Medicines with Regard to Professional Expertise**	
Tertiary Hospital	A,B,C,D,S	Specialist	A,B,C,D,S
Regional Referral Hospital	A,B,C,D	Medical Officer (MO)	A,B,C,D
District Hospital	A,B,C	Assistant Medical Officer (AMO)	A,B,C
Health Centre	A & B	Clinical Officer (CO)	A & B
Dispensary	A	Assistant Clinical Officer (ACO)	A

Hence, at tertiary level hospitals (S); the National, Zonal Referral and Specialized hospitals, all medicines in the NEMLIT may be stocked; as per hospital needs and specialists may prescribe all medicines listed in the NEMLIT. However, level (S) medicines are restricted to other experts. Implying that, a Medical Officers at tertiary hospital will be prescribe medicines listed A, B, C and D and Assistant Medical Officer A, B, C but not S.

At Regional Referral Hospitals (RRH) level, medicines listed as (A, B, C, D) will be stocked. Specialists at that level may prescribe medicines at level (A, B, C, D, S) as per their specialty areas e.g. cardiologist may prescribe cardiovascular diseases medicines at that level. Medical officer at RRH will prescribe medicines at level (A, B, C, D). If there is an Assistant Medical Officer at RRH allowed to prescribe medicines listed (A, B, C) and Clinical Officers (A, B).

- All health facilities in the public sector will adhere to the NEMLIT in procurement of medicines from MSD and other sources.
- The NHIF will adhere to the NEMLIT for reimbursement of medicines in both public and private health facilities.
- Special arrangement to quantify and procure medicines, which are not managed at specific health facilities but are needed due to presence of expertise as stated above; for that case the Hospital Pharmacists in collaboration with the Office of Chief Pharmacist shall facilitate the process.
- All medicines indicated for treatment of various diseases in the Standard Treatment Guidelines (STG) are listed in the NEMLIT.

Tables 3.5, 3.6, and 3.7 discriminate the missing formulations in some relevant therapeutic classes. In these tables, therapeutic alternatives existent in NDELIT 2021 in the same subgroups are described as drugs or formulations that are absent in LEMC 2021. In the therapeutic group “specific medication for neonatal care”, caffeine citrate, prostaglandin E and ibuprofen formulations were withdrawn, letting this population without appropriate alternatives for critical conditions.

Among medicines acting on the respiratory tract, only one formulation is missing, salbutamol sulfate 50 ug/mL in 5mL ampoule, and NDELIT presents more alternatives for asthma treatment than LEMC. In the group “anticonvulsant and antiepileptics”, suitable dosage forms and variety of strengths for common drugs (e.g. carbamazepine, diazepam, lorazepam, phenytoin) are missing, but NDELIT has some useful presentations of phenobarbital and valproic acid.

Table 3.6

Missing formulations for neonatal care, respiratory tract, central nervous system, and their therapeutic alternatives present only in NDELIT

Group	**Drug**	**Formulations missing in NDELIT**	**Therapeutic alternatives present only in NDELIT**
Specific medicines for neonatal care	Caffeine citrate Prostaglandin E	Injection: 20 mg/mL Oral liquid (solution): 20 mg/mL Solution for injection (E1: 0.5 mg/mL in alcohol; E2: 1 mg/mL) Solution for injection: 5 mg/mL	– – –
Medicines acting on the respiratory tract	Ibuprofen (Pedea) Salbutamol sulfate	5 mg/ml solution for injection Injection: 50 mcg/mL in 5-mL ampoule	– Ventolin 500 micrograms Injection
Anticonvulsants/ Antiepileptics	Carbamazepine Lorazepan Phenobarbital Phenytoin (sod. salt) Valproic acid (sodium valproate) Ethosuximide	Tablet (chewable): 100 mg; 200 mg. Injection: 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule. Oral liquid: 15 mg/5 mL. Tablet: 15 mg to 100 mg. Injection: 50 mg/mL (sodium) in 5 ml vial. Oral liquid: 25 mg to 30 mg/5 ml. Solid oral dosage form:25 mg; Oral liquid: 200mg/5 ml Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg. Oral liquid: 250 mg/5 mL.	Tablet (scored): 100 mg; 200 mg. diazepam (injection) - midazolam (injection) Injection 200 mg/ml; tabl 100mg Solid oral dos. form: 50 mg; 100 mg (sod.) Tabl.(chewable): 50 mg. Tablet (enteric-coated): 200 mg; 500 mg. –

Table 3.7

Missing formulations and therapeutic alternatives present only in NDELIT: antifungals, anthelminthics, antitrypanosomal

Group	**Drug**	**Formulations missing in NDELIT**	**Therapeutic alternatives present only in NDELIT**
Antifungal	Diethylcarbamazine Micafungin	Tablet (chewable): 400 mg. Tablet: 50 mg; 100 mg (dihydrogen citrate).	Ivermectin Tablet 3mg, 6mg
Anthelminthics	niclosamide praziquantel pyrantel	Tablet (chewable): 500 mg. Tablet: 150 mg; 600 mg. Oral liquid: 50 mg (as embonate or pamoate)/mL. Tablet (chewable): 250 mg (as embonate or pamoate)	Albendazole Suspension 100mg/5mL in 30mL bottle; A Tablet 200mg, 400mg, chewable
Antischistosomals and other antitrematode medicines	triclabendazole oxamniquine	Tablet: 250 mg. Capsule: 250 mg. Oral liquid: 250 mg/5 ml	praziquantel Tablet: 600 mg.
Cysticidal medicines	albendazole mebendazole praziquantel	Tablet (chewable): 400 mg. Tablet (chewable): 500 mg. Tablet: 500 mg; 600 mg	_
Access group antibiotics	amikacin amoxicillin cefalexin	Injection: 250 mg/mL (as sulfate) in 2 mL vial. Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial. Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate). Solid oral dosage form: 250 mg; 500 mg (as trihydrate). Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (anhydrous). Solid oral dosage form: 250 mg (as monohydrate).	- Amoxicillin Capsule (as trihydrate) 250mg; Dispersible A tablet 250mg, 125mg Cefalexin Capsule 250mg (as monohydrate) Powder for reconstitution 125/5mi; 250mg/mL

Table 3.8

Missing formulation and therapeutic alternatives present only in NDELIT: antituberculosis medicines, anti HIV drugs.

Group	**Drug**	**Formulations missing in NDELIT**	**Therapeutic alternatives present only in NDELIT**
Antituberculosis medicines	Ethambutol Isoniazid Rifampicin	Oral liquid: 25 mg/mL. Tablet: 100 mg; 400 mg (hydrochloride). Tablet (dispersible): 100 mg. Oral liquid: 20 mg/mL. Solid oral dosage form: 150 mg; 300 mg.	Rifampicin+Isoniazid Capsule/Tablet,150mg+75mg, 50mg+150mg
Antiviral	Aciclovir Didanosine Nevirapine [a] Lamivudine Zidovudine	Oral liquid: 40 mg/mL Buffered powder for oral liquid (solution): 100 mg, 167 mg, 250 mg Capsule (unbuffered enteric-coated): 125 mg, 200 mg Tablet (buffered chewable, dispersible): 25 mg, 50 mg, 100 mg, 150 mg, 200 mg Oral liquid: 50 mg/5 mL. Tablet (dispersible): 50 mg. a > 6 weeks Oral liquid: 50 mg/5 mL.	Aciclovir Cream 5%; Table 400mg; Injection 500mg/Vial Darunavir Tablet: 150 mg, 300 mg Lamivudine (3TC) Oral Liquid 50mg/mL; Tablet: 150mg Nevirapine (NVP) Oral liquid: 50mg/5mL; Tablet 50mg **A** (dispersible); 200mg Ritonavir Oral liquid 400mg/5mL; Tablet 25mg; 100mg
Medicines for Hepatitis-B Medicines for Hepatitis C	Entecavir Daclatasvir* Daclatasvir + Sofosbuvir Glecaprevir + Pibrentasvir Sofosbuvir* Glecaprevir + pibrentasvir	Oral liquid: 0.05 mg/ mL Tablet: 0.5 mg; 1 mg Tablet: 30 mg; 60 mg (as hydrochloride). Tablet: 60 mg + 400 mg. Granules: 50 mg + 20 mg in sachet. Tablet: 100 mg + 40 mg. Tablet: 200 mg; 400 mg. *Pangenotypic when used in combination with daclatasvir Tablet: 200 mg + 50 mg; 400 mg + 100 mg	Tenofovir disoproxil fumarate Tablet: 300 mg Ledipasvir Tablet 90mg Tablet 600mg Tablet 400mg Ribavirin Sofosbuvir

The lack of medicine formulations suitable for children is a worldwide concern, taken into consideration in some developed countries, as well as multilaterally by organizations such as the WHO.

The present work performed an inventory of the missing essential medicines in suitable formulations for children in NDELIT, using LEMC as a reference. Some of the drugs completely absent in NDELIT but present in LEMC have minimal or no importance for Tanzanii children, but others are useful systemic antibiotics, such as vancomycin, ampicillin, and cloxacillin (or its equivalent oxacillin, widely used in Tanzanii).

This was not an exhaustive quantitative or qualitative analysis regarding which drugs and formulations should be considered essential for Tanzania children, to describe the lack of drugs and formulations suitable for children as a relevant problem that deserves the attention of health policy makers. It is well- known that the absence of appropriate medicines and formulations for children (drugs duly studied in children, suitable dosage form, and strength) leads to unlicensed and off-label use of medicines and/or to the use of less safe or effective drugs. The lack of specific medication for neonatal treatment, as when comparing NDELIT to LEMC, forces the use of magistral or extemporaneous preparations, and sometimes the replacement of a drug by a more toxic substitute.

An example of the former is the use of prepared caffeine citrate as a respiratory stimulant, and the latter is the use of indomethacin instead of ibuprofen for patent ductus arteriosus. Another example related to neonates is the absence of the antimicrobials ampicillin and gentamicin in Rename, which compromises adequate treatment of Enterococcus sp. systemic Listeria monocytogenes infections.

In our study, dosage forms studied included antimicrobial, anti-asthma and analgesics, essential drugs for severe clinical conditions such as seizure disorders (anticonvulsants), cardiovascular disease and tuberculosis, as well as drugs for vulnerable age groups such as newborns.

CONCLUSIONS TO CHAPTER III

1. Available data show that while the national list of essential medicines has become more “child-friendly” with each revision, children's access to these essential medicines has not improved.

2. Tanzania’s EML has more unique molecules compared to the WHO’s EMLC (593 in Tanzania vs. 350 in WHO). The number of NCD medicines is higher in the Tanzania’s EML compared to the WHO EMLC (110 in Tanzania vs. 17 in WHO). Of these, at least 116 medicines are present in the Tanzania EML and absent from the WHO EML.

3. A similar number of cancer drugs are included in both lists (30 in WHO vs. 36 in Tanzania), however only eight molecules are in common. The Tanzania EML has a higher number of drugs for respiratory conditions compared to the WHO EML (31 in Tanzania vs. 5 in WHO).

4. To address the large number of pediatric formulations that need to be included in the list, the development of a specific list of essential medicines for children in Tanzania appears to be a viable solution. Such an instrument could be part of a broader incentive policy development and production of medicines for children in the country.

5. The development of a pediatric-specific essential medicines list potentially increases the awareness of the need for pediatric-specific medications and formulations, and highlights areas of priority where medications are lacking. Providing access to these formulations according to the need and promoting their rational use in children are concomitant challenges to be addressed by Tanzania health policies.

GENERAL CONCLUSIONS

1. The World Health Organization's Essential Medicines List for children guides the rational selection and use of medicines in children aged 0-12 years. Essential medicines can be defined as medicines necessary to prevent, treat or manage the most prevalent diseases in a population. Essential medicines are divided into two groups: a 'core' list meeting needs for a basic healthcare system and a 'complementary' list requiring specialist medical facilities.

2. The WHO Essential Medicine List for children is used for promoting access to medicines. The age-appropriateness of enteral (oral and rectal) formulations for children depend on their adaptability/flexibility to allow age- or weight-related doses to be administered/prescribed and the child's ability to swallow, as appropriate.

3. WHO's national list of EMs has been updated every two years since 1977, but in 2007 a separate list of EMs for children under 12 was created. In 2021, the 8th list of essential medicines for children was released, which includes 350 items of medicines, for comparison, the 1st list consisted of only 264 drugs.

4. The World Health Organization in 2021 published a new edition of the Model Lists of Essential Medicines and Essential Medicines for Children, their 22nd and 8th editions, respectively. The updated lists included 20 new drugs for adults and 17 for children, as well as new indications for the use of 28 drugs. The changes recommended by the Expert Committee increase the number of medicines needed to meet the basic needs of the public health care, up to 479 on the first list and 350 on the second list (for children).

5. It has been established that less than 50% of drugs have established effectiveness and safety for children, which, in turn, leads to irrational (off label, unlicensed drug) prescriptions and ensures fairly high rates (up to 10%) of hospitalization as a result of drug complications.

6. It was established that the main share of drugs for children included in the WHO List is formed from liquid medicinal forms (59%). The main share of drugs is given in the form of syrups 35%, the second place is occupied by tablets, followed

by drops and suppositories 12% each. According to the dosage forms of the National List of EM, the predominance of solid dosage forms is established, namely: tablets and capsules (96%).

7. In Tanzania 50% of essential medicines had one or more registered products. However essential medicine products accounted for only 37% (1312/3590) of all registered products in Tanzania, with non-essential medicines comprising 2278 registered products. The essential medicines that were not registered are described by class 33% of registered essential medicines Tanzania had either one or two products only.

8. In Tanzaia there is no separate EMLs for children: The main list is made ‘child-friendly’ by adding paediatric formulations and strengths for medicines common to adults and children, and including medicines exclusively for children (eg, specific medicines for neonatal care).

9. Tanzania’s EML has more unique molecules compared to the WHO’s EMLC (593 in Tanzania vs. 350 in WHO). The number of NCD medicines is higher in the Tanzania’s EML compared to the WHO EMLC (110 in Tanzania vs. 17 in WHO). Of these, at least 116 medicines are present in the Tanzania EML and absent from the WHO EML.

10. Most of the recommended essential medicines in the 2021 EML Tanzania and the 2021 WHO Children's List not appropriate for children under 6 years of age. Age-inappropriate drugs must be manipulated prior to administration, which can lead to safety and efficacy issues. Assessing the age-appropriate formulations of medicines to be included on the EMLc can improve access to better quality medicines for children in the future.

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Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of social pharmacy

Level of higher education master's

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Social Pharmacy

_____
Alina VOLKOVA
"28" of September 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Sylvester Janet JOSEPH

1. Topic of qualification work: « Study of modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children», supervisor of qualification work: Lyubov TERESHCHENKO, PhD, assoc. prof.,

approved by order of NUPh from "06" of February 2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: April 2023.

3. Outgoing data for qualification work: regulatory and legislative acts on the therapy of children in the world, the State Register of Medicines of Tanzania; the legislative framework of EU countries, the USA and Tanzania in accordance with the regulation of the introduction of drugs for children; List of EM for children WHO, BNDF, Tanzania National EM List.

4. Contents of the settlement and explanatory note (list of questions that need to be developed:
conduct an analysis of the current state of pharmaceutical care for children;
to analyze the legislative acts regulating the development and introduction of medicinal forms in the world; to conduct an analysis of the National List of EM of Tanzania;
conduct an analysis of the List of EMs for children of WHO;
conduct an analysis of BNFD;
to carry out a comparative analysis of the range of drugs of the List of drugs for children of WHO, the National list of drugs of Tanzania.

5. List of graphic material (with exact indication of the required drawings):
Tables – 15, schemes – 9.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Lyubov TERESHCHENKO, associate professor of higher education institution of department of social pharmacy	30.09.22	30.09.22
2	Lyubov TERESHCHENKO, associate professor of higher education institution of department of social pharmacy	15.11.22	15.11.22
3	Lyubov TERESHCHENKO, associate professor of higher education institution of department social of pharmacy	23.12.23	23.12.23

7. Date of issue of the assignment: «_ 28_ » of September 2022.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Analyze the current state of pharmaceutical care for children	*October 2022*	**done**
2	Analyze the legislative acts regulating the development and implementation of medicinal forms in the world	*November-December 2022*	**done**
3	Conduct a comparative analysis o between the World Health Organization list of essential medicines for children (8th list, 2021) and the Tanzania list of essential medicines (sixth edition 2021).	*January-February 2023*	**done**
4	Registration of a qualification work according to the general requirements	*March 2023*	**done**
5	Preparation of the report and multimedia presentation in official protection of a master's thesis	*April 2023*	**done**

An applicant of higher education _____ Sylvester Janet JOSEPH

Supervisor of qualification work _____ Lyubov TERESHCHENKO

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі соціальної фармації**				
Сільвестер Дженет Джозеф	Дослідження сучасних підходів щодо формування нормативних переліків для надання фармацевтичної допомоги дітям	Study of modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children	доцент Терещенко Л. В.	доцент Бондарєва І. В.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 113206 від « 10 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Сільвестер Дженет Джозеф, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Дослідження сучасних підходів щодо формування нормативних переліків для надання фармацевтичної допомоги дітям / Study of modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,

професор **Інна ВЛАДИМИРОВА**

2%

30%

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy
Sylvester Janet JOSEPH
on the topic: « Study of modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children »

Relevance of the topic. Rational pharmacotherapy in children remains one of the most urgent problems in medicine and pharmacy. The problem of this issue is the ignoring of the ethical and deontological principles of pediatric pharmacology, namely: numerous drugs that are used in adults are, by the same analogy, used in children's practice, which, accordingly, is unacceptable in the conditions of the modern level of pharmacy development. To date, numerous scientific authors have highlighted a number of features of the child's body that affect the kinetics and metabolism of drugs in different age groups, this is undoubtedly reflected in the pharmacotherapeutic effectiveness of treatment. Therefore, the research of modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children is relevant.

Practical value of conclusions, recommendations and their validity. The results of the conducted research established that the British National Formulary consists of 9 INNs. The absence of drugs included in the WHO list significantly affects the quality of pharmaceutical care for children, therefore it is necessary to revise and supplement the National List of EM of Tanzania with drugs for children, as well as support for the creation of a domestic formulary for children.

Assessment of work. The work is done and designed properly and deserves a positive assessment.

General conclusion and recommendations on admission to defend. During the performance of the work, the procurer Sylvester Janet JOSEPH demonstrated the ability to work with literature, summarize the obtained results, draw conclusions based on the conducted research. Thus, the qualifying work meets all requirements for qualifying works and can be submitted for defense.

Scientific supervisor _____ Lyubov TERESHCHENKO

«06» of April 2023

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy
Sylvester Janet JOSEPH
on the topic: « Study of modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children»

Relevance of the topic. The problem of polypharmacy is especially relevant in pediatrics: the risk of complications increases when several drugs are prescribed at the same time against the background of physiologically determined slowed metabolism. The principles of rational pharmacotherapy in pediatric practice should be built exclusively taking into account the characteristics of the child's body, which will greatly limit the possibility of developing direct adverse reactions and allow for the most effective and safe treatment.

Theoretical level of work. In the qualifying work, the peculiarities of pharmacotherapy in children were investigated, the List of EMs for children of WHO and the National List of EMs of Tanzania were analyzed. A comparative analysis of regulatory lists and BNFD and the State Register of Pharmaceuticals of Tanzania for drugs used in pediatrics was conducted.

Author's suggestions on the research topic. The implementation of the Children's State Formulary will significantly reduce the side effects of drugs that are prescribed for treatment, but do not have clinically proven effectiveness among children.

Practical value of conclusions, recommendations and their validity. Problems of rational pharmacology of children's diseases should be solved taking into account both medical and biopharmaceutical aspects. At the same time, models of state regulation of the circulation of drugs for children require a balanced and scientifically based approach.

Disadvantages of work. The work is overloaded with theoretical material. This remark fundamentally does not change the evaluation of the work.

General conclusion and assessment of the work. On the basis of the clearly formulated tasks, the complex of research methods used, and the evaluation of the results of the conducted research, Sylvester Janet JOSEPH managed to achieve the goal set in the qualification work. Thus, the qualification work meets the requirements and can be recommended to of protection at the Examination Commission of the NUPh.

Reviewer _____ Irina BONDAREVA

«13» of April 2023

ВИТЯГ
з протоколу засідання кафедри соціальної фармації
№ 12 від «20» квітня 2023 року

ПРИСУТНІ: зав. каф. доц. Волкова А. В., доц. Кубарєва І.В., доц. Овакімян О.С., доц. Болдарь Г.Є., доц. Корж Ю.В., доц. Терещенко Л.В., доц.Гавриш Н.Б., доц. Калайчева С.Г., ас. Пилюга Л.В., ас. Сєврюков О.В., ас. Сурікова І.О., ас. Тарасенко Д.Ю., ас. Ноздріна А.А.

ПОРЯДОК ДЕННИЙ: Про представлення до захисту в Екзаменаційній комісії кваліфікаційних робіт.

СЛУХАЛИ: завідувачку кафедри доц. Волкову А. В. з рекомендацією представити до захисту в Екзаменаційній комісії кваліфікаційну роботу здобувача вищої освіти спеціальності 226 Фармація, промислова фармація Сильвестр Дженет Джозеф на тему: «Дослідження сучасних підходів щодо формування нормативних переліків для надання фармацевтичної допомоги дітям».

Науковий керівник: к. фарм. н., доцент кафедри СФ Терещенко Л.В.

Рецензент: к. фарм. н., доцент кафедри ФММ Бондарева І.В.

ВИСТУПИЛИ: доц. Корж Ю.В., доц. Болдарь Г.В., доц. Волкова А. В. висловили рекомендації до кваліфікаційної роботи Сильвестр Дженет Джозеф

УХВАЛИЛИ: Рекомендувати до захисту в Екзаменаційній комісії кваліфікаційну роботу здобувача вищої освіти Сильвестр Дженет Джозеф на тему: «Дослідження сучасних підходів щодо формування нормативних переліків для надання фармацевтичної допомоги дітям».

Завідувачка каф. СФ, доцент _____ Аліна ВОЛКОВА

Секретар, асистент _____ Альміра НОЗДРІНА

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Сільвестер Дженет ДЖОЗЕФ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Study of modern approaches to the formation of regulatory lists for the provision of pharmaceutical care to children».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Сільвестер Дженет ДЖОЗЕФ під час виконання кваліфікаційної роботи вивчив і проаналізував значний обсяг літератури та нормативно правових актів по темі. Проведений аналіз підтверджує актуальність досліджень і висуває необхідність їх проведення.

Керівник кваліфікаційної роботи _____ Любов ТЕРЕЩЕНКО

«06» квітня 2023 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Сільвестер Дженет ДЖОЗЕФ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
соціальної фармації _____ Аліна ВОЛКОВА

«20» квітня 2023 р.

Qualification work was defended

of Examination commission on

« ___ » _____ 2023

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /