4.4 Prospects for the creation of drugs for external use through the prism of marketing research of the pharmaceutical market of Ukraine

Despite the priority task of the pharmaceutical industry "Development of import-substituting industries in Ukraine and replacement of imported drugs with domestic ones, including biotechnological drugs and vaccines for 2011-2021" remains relevant. economic availability of medicines and will gradually solve the problem of import substitution. This concept is becoming more relevant especially in the global economic crisis.

Wound healing and wound infection is the oldest medical problem that remains unresolved to this day. According to the literature, purulent-necrotic soft tissue diseases occupy one

from the leading places among surgical diseases: patients of a surgical profile with purulent-inflammatory diseases make 35-45%, and postoperative purulent complications arise in 24-30% of cases.

The armed conflict in Ukraine has led to the actualization of combat surgical trauma, both for the military and the national health care system.

Wound is a mechanical violation of the integrity of the skin, mucous membranes, as well as tissues and organs that are located deeper below them, accompanied by the development of local, regional and general disorders.

In general, the wound process is a universal reaction of the body that develops in response to damaging factors and is a coordinated cellular and biochemical processes, with a complex set of biological reactions, the ultimate focus of which is wound healing. The wound healing process involves certain phases that overlap over time and cannot be separated. This distribution is artificial, but it reflects the chronological sequence of events that characterize wound healing.

Treatment of purulent wounds is a complex and multi-component process, the main objectives of which are determined by the need to influence the leading factors of pathogenesis:

1) rapid wound cleansing;

2) suppression of wound microflora;

3) reduction of inflammatory-infiltrative processes in the wound;

4) acceleration of reparative processes.

A fundamental approach to the treatment of purulent wounds at the present stage

there is a pathogenetic orientation according to the phase of the wound process, which includes the following stages: active surgical treatment (debridement); additional treatment of the postoperative wound; early closure of the wound defect; wound drainage; general and local antibacterial therapy; elimination of factors that slow down healing.

Based on this, we conducted marketing research on the pharmaceutical market of Ukraine and studied the factors influencing the effectiveness of the drug.

A gunshot wound is damage to tissues and organs with violation of the integrity of their cover - skin, mucous or serous membrane caused by firearms, and is characterized by a zone of primary necrosis and changes in surrounding tissues, which cause the formation of foci of secondary necrosis, as well as primary microbial contamination

The arsenal of dermatological medicines is one of the dynamic segments of the pharmaceutical market. Despite the popularity of the use of dermatological preparations, there is an uneven distribution of their production according to the areas of application. Therefore, marketing research of registered medicines makes it possible to identify free areas for filling with a certain assortment.

The materials for the study were the Register of Medicines Registered in Ukraine and other electronic and paper official sources of information [320, 321]. We used generally accepted systemic, graphical and structural analysis, methods of observation, comparison and generalization.

During the study, all registered dermatological medicinal products were divided into pharmacological groups according to the ATC classification system (Anatomical Therapeutic Chemical classification system), developed and recommended by the WHO Regional Office for Europe.

It was established that the range of dermatological medicines (for 2020) approved for use in Ukraine amounted to 366 trade names (315 excluding dosage form).

On fig. 1 shows the distribution of dermatological drugs according to the ATC classification.

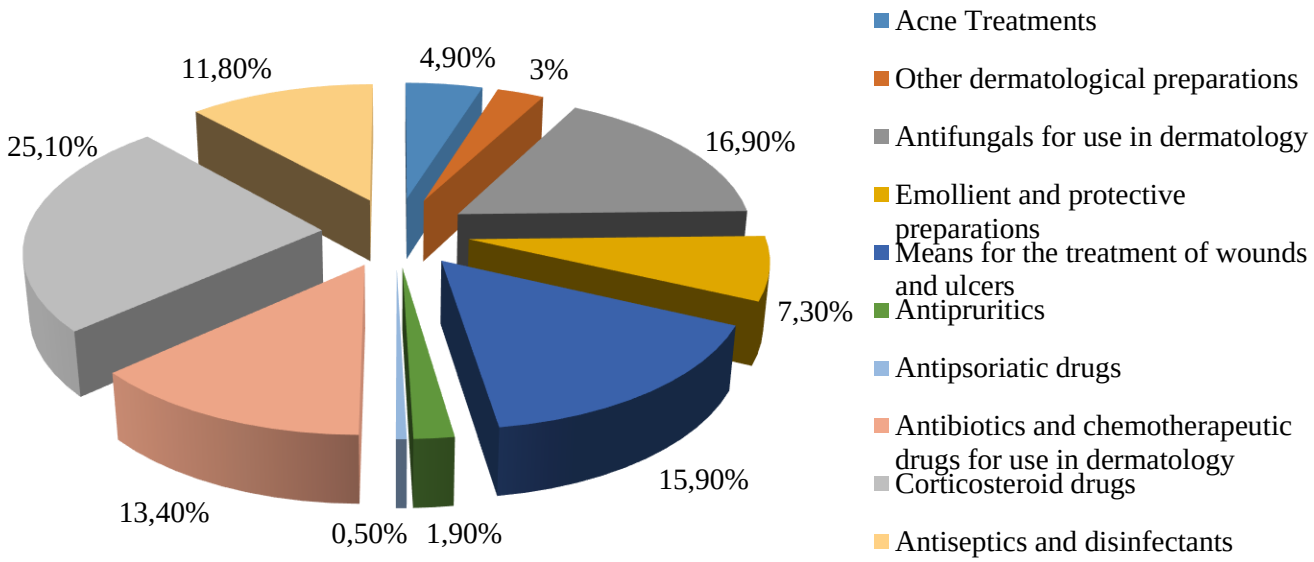

Figure 1. Segmentation of dermatological drugs according to the ATC classification system

The study shows that the pharmaceutical market of Ukraine is dominated by imported drugs – 58,2%, including 6,6% from neighboring countries.

Medicines from 32 countries are registered in Ukraine. Imported dermatological drugs enter the Ukrainian market from countries, among which a significant part is occupied by Germany (19,7%), India (15,0%), Poland (10,8%), Croatia and Russia (6,1% each). Countries supplying 1-3 drug names account for 10,8% of the total number of suppliers of foreign-made dermatological drugs (Argentina, Bulgaria, Bangladesh, Estonia, Canada, China, Cuba, Moldova, Portugal, the Palestinian Territory, Slovenia, USA, Turkey, France).

The structuring of the market for imported dermatological medicines depending on the manufacturing country is shown in Figure 2.

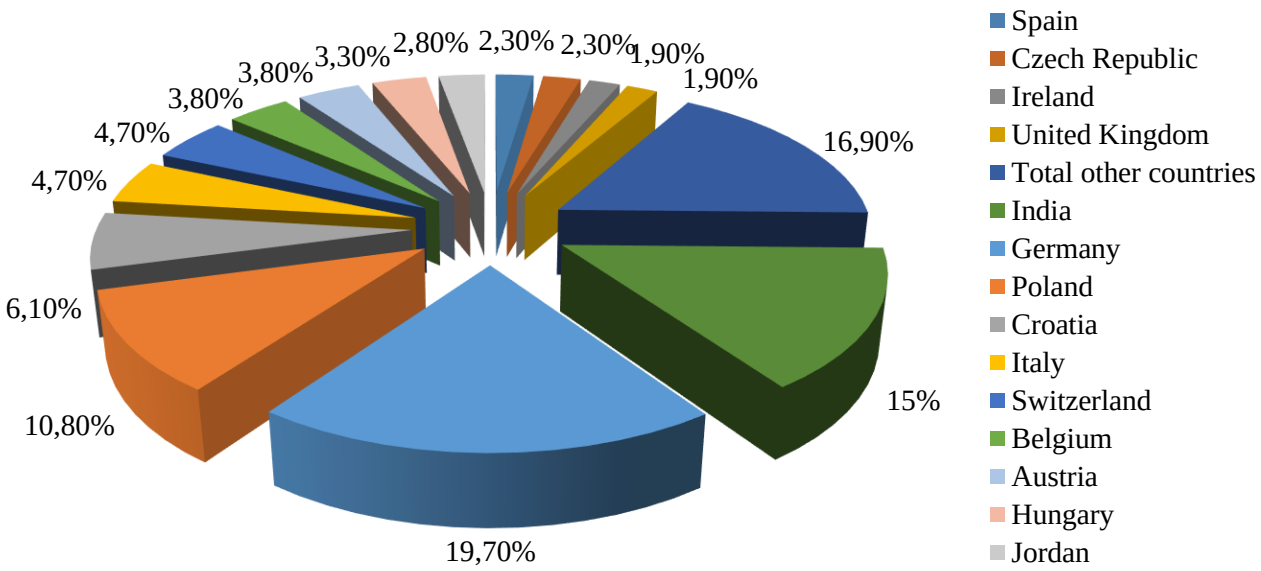

Figure 2. Structuring of imported dermatological medicines depending on the country of origin

In Ukraine, dermatological medicines are produced by 37 pharmaceutical companies.

During the segmentation of the assortment of dermatological preparations by dosage forms, it was found that ointments (39,1%) and creams (29,8%) dominate, which together make up the bulk of the assortment (Fig. 3). A promising LF in the form of an aerosol/spray deserves attention, which in recent years has increased its presence (3.5%) in the Ukrainian market. This niche is also filled by Ukrainian pharmaceutical companies.

A promising LF in the form of an aerosol/spray deserves attention, which in recent years has increased its presence (3,5%) in the Ukrainian market. This niche is also filled by Ukrainian pharmaceutical companies.

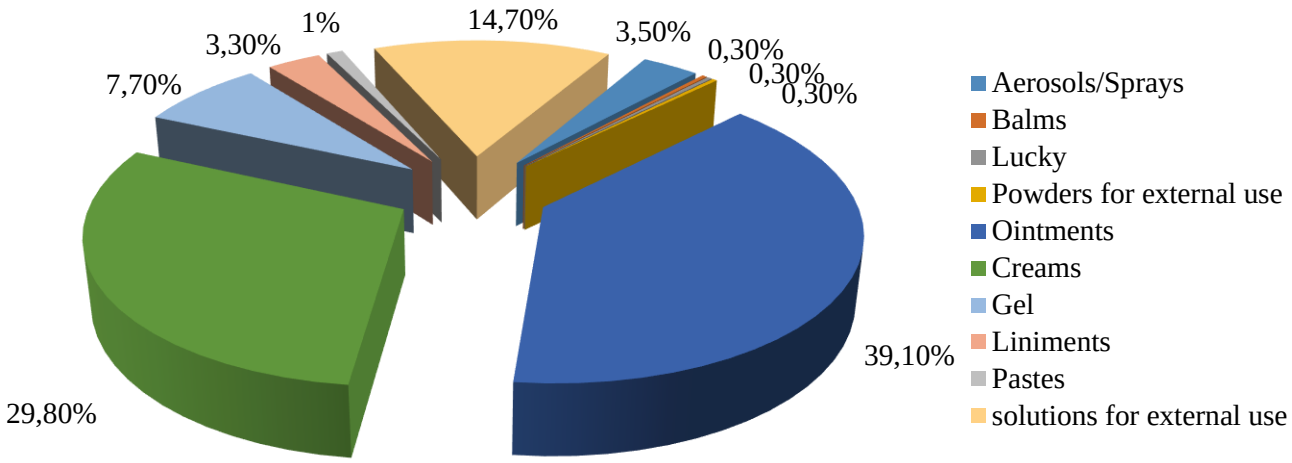

Figure 3. Structure of drug group D depending on dosage form

The next stage of the study was a detailed study of the range of drugs in the subgroups of group D according to the form of release, country of manufacture, leading active substances and their combinations.

The analysis showed that the group D01 "Antifungal drugs for use in dermatology" consists of 62 trade names (16,9% of the total number of dermatological drugs) mainly of foreign production – 64,5%. Imported drugs of this group are supplied to the Ukrainian market from countries, among which India occupies a significant part – 9 drugs (14,5%), the Czech Republic – 5 drugs (8%), Switzerland and Italy – 4 each (6,5% each), Hungary – 3 (4,8%). Spain and Germany registered 2 names each (3,2% each). Countries such as Bulgaria, Moldova, Russia, Belgium, the Palestinian Territory, Poland, France provide 1 name of medicines for the Ukrainian market.

In Ukraine, 14 pharmaceutical companies work with a range of antifungal agents for topical use. In the course of segmentation of the assortment of drugs of the D01 group according to the dosage form, it was found that imported creams account for almost half of the assortment (Fig. 4).

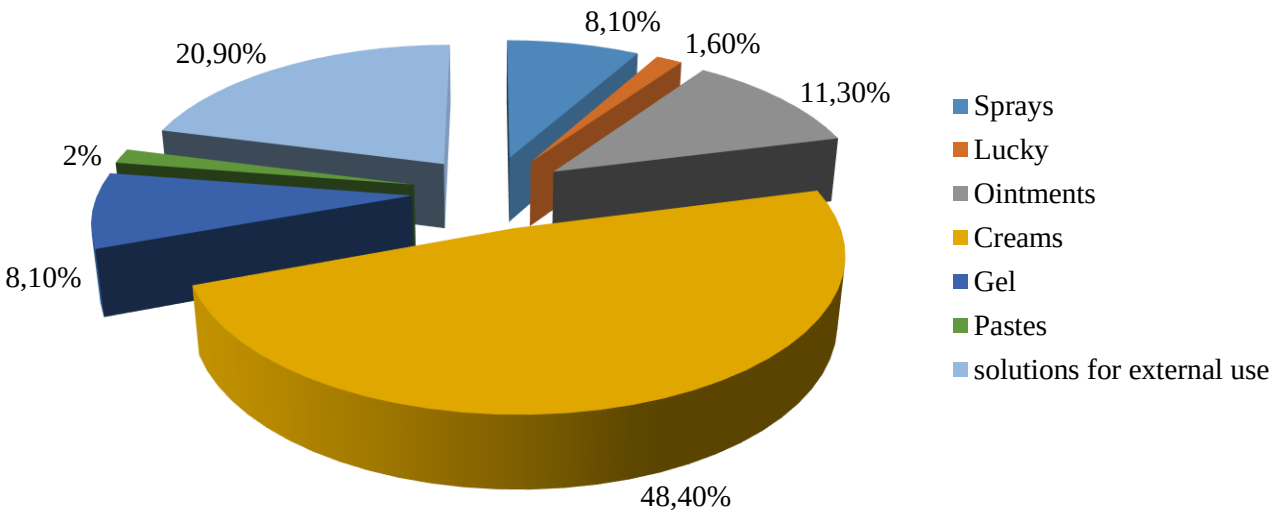

Figure 4. The structure of preparations of group D01 depending on the nature of the dispersed system

Solutions occupy 20,9%, but it should be noted that these are mostly well-known alcohol solutions, which are also duplicated by domestic manufacturers (salicylic acid solution, calendula tincture, etc.).

Group D01 consists of subgroups: Antibiotics (D01AA), Imidazole and triazole derivatives (D01AC), Other topical antifungals (D01AE).

In table. 1 according to the ATC classification lists the active ingredients representing this group. As follows from Table. 1 in group D01 among the active substances, the leading position is occupied by terbinofine and clotrimazole, on the basis of which 16 and 10 drugs are presented, respectively.

Table 1.

The structure of the pharmaceutical market of Ukraine of group D01

ATC code	International generic name	Number of medicines, pcs		
		imported	Ukrainian	Total
D01A A01	Nystatin	–	–	–
D01A A02	Natamycin	2	–	**2**
D01A C01	Clotrimazole	7	3	**10**
D01A C02	Miconazole	–	2	**2**
D01A C03	Econazole)	1	1	**2**
D01A C05	Isoconazole	1	–	**1**
D01A C08	Ketoconazole	2	1	**3**

D01A C10	Bifonazole	1	–	**1**
D01A C11	Oxiconazole	1	–	**1**
D01A C12	Fenticonazole	1	–	**1**
D01A C13	Omoconazole	2	–	**2**
D01A C14	Sertaconazol	2	–	**2**
D01A C15	Fluconazol	–	–	–
D01A C51	Clotrimazole, combinations	–	2	**2**
D01A C55	Isoconazole, combinations	1	–	**1**
D01A C60	Bifonazole, combinations	1	–	**1**
D01A E12	Salicylic acid	1	6	**7**
D01A E15	Terbinafine	12	4	**16**
D01A E20	combinations	1	–	**1**
D01A E22	Naftifine	2	–	**2**
D01A E50	Other drugs	1	1	**1**
D01A E54	Undecylenic acid, combinations	4	–	**4**

In this group, there are only 3 drugs of combined action, of which 1 Ukrainian-made ointment and 2 imported drugs - Mikoseptin ointment (Czech Republic), Travacort cream (Italy/Germany).

Group D02 – "Preparations with emollient and protective action", has 24 trade names (7,3% of the total number of dermatological drugs). The D02 group is dominated by Ukrainian drugs (70,8%). But part of the domestic assortment is the duplication of simple recipes by manufacturers: vaseline (4), glycerin (4), salicylic ointment (3), zinc ointment (3) and salicylic-zinc paste (1). Imported drugs of the D02 group are supplied to Ukraine by Switzerland – 3 items, which is 12,5% of the dermatological drugs of this group, and Germany, the USA, Jordan and Egypt have registered 1 drug each.

During the distribution of drugs by dosage form, it was found that more than half (54,2%) of the total number of items are ointments (Fig. 5).

Among the leading active ingredients in foreign preparations of this group, urea occupies a significant place (Table 2). Foreign manufacturers presented only 3 combined preparations in this group: Kerasal ointment (Switzerland), Sudocrem (Ireland), Kolomak solution (Egypt).

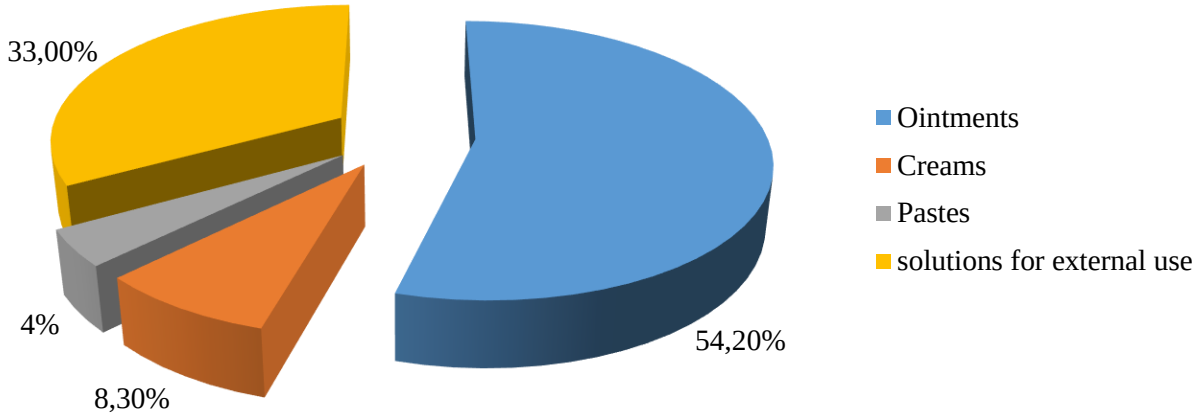

Figure 5. The structure of drugs of group D02 depending on the nature of the dispersed system

Table 2.

The structure of the Ukrainian pharmaceutical market of the D02 group

ATC code / Group		International generic name	Number of medicines, pcs		
			Imported	Ukrainian	Total
D02A B Zinc preparations	D02A B01	*Zinc oxide*	1	3	**4**
	D02A B51	*Zinc oxide*, combinations	1	–	**1**
D02A C Preparations of fats and soft paraffin		*Vaseline*	–	4	**4**
D02A E Urea preparations	D02A E01	*Carbamide*	5	1	**6**
D02A F Salicylic acid preparations		*Salicylic acid*	2	4	**6**
D02A X Other preparations with emollient and protective action		*Glycerol*	–	5	**5**

In the large group D03 – "Means for the treatment of wounds and ulcers" (58 trade names), domestic drugs predominate – 58,6%, which are produced by 24 pharmaceutical enterprises. Imported drugs are supplied from such countries as Germany – 8 items, Austria – 4, Croatia – 3. Hungary, Russia, Germany/Switzerland have registered 2 drugs each, and Cuba, Bulgaria and Poland – 1 each.

Ointments make up about half of the entire range of this group (39,7%), solutions – 31,0%, creams – 12,0%, gels – 6,9%, aerosols – 3%, another range is presented by 1 drug (spray, foam, juice for external use).

A variety of active substances have been established in this group, but dexpanthenol, which is part of 12 medicines, and levomycetin, methyluracil,

miramistin, and zinc hyaluronate can be distinguished. The assortment consists mainly of domestic preparations, including repeat calendula ointment and calendula tinctures. Looking at 13 combination medicines group D03, it can be noted that these are drugs mainly of Ukrainian production: Aekol oil solution, Altan ointment, Livian aerosol, Algofin ointments, Vundehil, Methyluracil with Miramistin, Mefenat, Nitacid-Darnitsa, Pantestin-Darnitsa gel, Thiotriazolin ointment. With a more detailed analysis, it turns out that the combined Levomekol ointment is duplicated by three Ukrainian and one Russian enterprises. In addition, foreign products are represented by such drugs of complex action as Alantan Plus (Poland), Acerbin (Austria), Ebermin (Republic of Cuba), Contractubex (Germany). In the small group D04 – Antipruritic drugs (7 items), combined drugs are represented by only 2 Ukrainian-made ointments – Ketotsin and Menovazin.

Group D05 – "Antipsoriatic agents" consists of only 2 monocomponent ointments of foreign companies.

In group D06 – "Antibiotics and chemotherapeutic drugs for use in dermatology" there are 49 drugs (13,4% of the total number of dermatological drugs) mainly of foreign production (61%). Germany supplies 6 drugs of this group (12%), Russia, Jordan, Great Britain – 3 (6%) each, Poland – 2 items (4%), and the rest – 1 drug each. 19 drugs of the D06 group are produced by 12 Ukrainian enterprises.

The analysis revealed that in the D06 group, ointments and creams make up almost the entire range of the group – 77,6%, and gels and liniments – 8,2% and 6,1%, respectively.

In the numerous assortment of this group there are only 8 combined drugs, 6 of which are produced by Ukrainian pharmaceutical enterprises: Inflarak, Oflokain-Darnitsa, Streptonitol-Darnitsa, Levosin, the latter is also supplied from Russia. There is also an ointment of combined action of foreign production - Baneocin (Austria). Among the APIs in this group, acyclovir (8), fusidic acid (5), silver salts (silver sulfadiazine, silver sulfatiazole) (5) are in the lead.

Group D07 "Corticosteroids for use in dermatology" is the largest of all groups D and is represented by 92 items, which is 25,1% of the total number of dermatological

drugs. The analysis showed that in this group, mainly drugs of foreign production – 81,5%. Almost half of imported dermatological medicines are supplied to the Ukrainian market by Germany and Poland – 16 medicines each (21,3% each), a significant part of the market is occupied by Croatia and India – 8 medicines each (10,7%), Belgium supplies 7 medicines (9,4%), Italy – 6 (8%).

Group D08 – "Antiseptics and disinfectants" consists of 43 medicines, mostly Ukrainian-made (67,4%). These are mainly ointments and liniments, while Balsamic liniment (according to Vishnevsky) is produced by nine Ukrainian manufacturers, and boric ointment – by four. Foreign manufacturers supply combined medicines: Instillagel (Germany/Latvia), Bepanten Plus (Germany/Switzerland), Vokadin (India) in two concentrations, Septiklin (India), Skindez (India). Among the active ingredients, the leading position is occupied by povidone iodine, ichthyol, xeroform, chlorhexidine.

A small assortment of group D10 “Medications for the treatment of acne” (18 medicines) is represented mainly by gels. The following APIs can be distinguished: azelaic acid, which is contained in 5 drugs, clindamycin – in 5, adapalene – in 3, erythromycin – in 3 drugs. Three Ukrainian pharmaceutical companies produce sulfuric ointment. Only foreign-made combined drugs presented on the market: Adatsin (India), Deriva S (India), Clearan Zinc (India), Isotrexin (Ireland).

In group D11 – "Other dermatological preparations" (11 items), duplication of drugs (Pasta Teymurova) was established by two domestic manufacturers. The other two preparations with a combination of active substances of plant origin are Arkalen ointment (Poland) and Perfect cream (India).

The analysis of the objects of study showed the monocomponent nature of drugs of group D, and drugs of combined action account for 21,0%.

As a result of the study, we have identified niches in the pharmaceutical market of Ukraine that are not sufficiently filled with Ukrainian-made medicines. Marketing research shows the relevance of the development of dermatological medicines by Ukrainian manufacturers. Despite a significant range of soft drugs for wound treatment, the issue of creating soft drugs with complex action remains relevant. Thus,

the development and introduction into production of combined soft drugs for the treatment of the wound process is promising.

In the future, we analyzed the dynamics of sales of drugs under international non-proprietary names (INN), which are often used to treat wounds. Drugs containing ceftriaxone (J01D D04), dioxidine (J01X X13**), methyluracil (A14B), erythromycin (J01F A01), decamethoxine (D01AJ10), lidocaine (D04A B01) and metronidazole (J01X D) were selected for analysis. forms for external use. These drugs (drugs) in the pharmaceutical market of Ukraine are present both in the form of single drugs and in combinations. The dynamics of sales of drugs under the international non-proprietary name (in packaging) for the last 5 years are given in table. 3.

Table 3.

Dynamics of sales of drugs for INN in packages for 2015 – 2019

Drugs for INN	Years				
	2015	2016	2017	2018	2019
Decamethoxin	862975	1111871	1151582	1128918	940776
Dioxidine	129407	136781	139580	133416	123643
Lidocaine	23 893	32 199	37 046	42 061	50 176
Methyluracil	143 688	132 095	126 072	14 373	0
Erythromycin	120	0	0	0	0
Metronidazole	88277	99071	118351	131290	158527
Lidocaine + ofloxacin	416344	465782	503558	546845	550852
Methyluracil + Miramistin	98658	166949	215873	317499	363641
Dioxidine + lidocaine	173307	198505	223291	245001	266010
Methyluracil + sulfadimethoxine + trimecaine + chloramphenicol	143430	138 987	151 604	151 301	150 036
Methyluracil+ chloramphenicol	2140435	2221198	2445792	2845071	2946537
Total	4220535	4703438	5112750	5555775	5550198

Data analysis table. 3 showed that the leaders in sales of this segment are drugs containing antiseptics or antimicrobial drugs – chloramphenicol, decamethoxine, ofloxacin, dioxidine and metronidazole. More than half of the segment is chloramphenicol in combination with methyluracil. In the form of mono-drugs

antimicrobial drugs are decamethoxine, dioxidine and metronidazole. Erythromycin has not been available in this segment for the last four years.

Most often, antimicrobials are combined with anesthetics (lidocaine) or wound-healing agents (methyluracil). The structure of sales shows that combined drugs are the most popular.

Mild drugs play an important role in the treatment of wounds due to the ability to directly affect the leading factors of pathogenesis – pathogens, necrotic-inflammatory and reparative processes in the wound.

According to the State Pharmacopoeia of Ukraine (SPU), Soft drugs for external use are divided into ointments (water-emulsion, hydrophilic, hydrophobic), creams (lipophilic, hydrophilic), gels (lipophilic, hydrophilic), pastes, poultices, medical and skin patches , as well as liniments (ointments, creams, gels and pastes with the ability to melt at body temperature).

The choice of drug composition, dosage form and technological methods is made at the stage of pharmaceutical development, where the foundations of quality, efficacy and safety of the drug are laid. The main conditions of action of topical drugs are the release of active ingredients from the dosage form and penetration through biological membranes to the lesion.

Carrier bases are important components of Soft Medicines, as they make up 90% or more of the total mass and affect the activity of substances and rheological properties of the dosage form.

Rationale for the choice of carrier base in the creation of soft drugs, along with the choice of active substances and their concentration, is one of the basic fragments of the study, because it is the basis to the greatest extent affects the rate and completeness of active substances, as well as provides optimal consistency of drugs and its consumer characteristics.

The results of numerous studies show that the use of ointments based on hydrophilic and emulsion bases, which are characterized by dehydrating action and the ability to effectively conduct active substances to wound canals and cavities, is clinically justified for the local treatment of the wound process.

An important feature of drugs for the local treatment of the wound process is that not only the active substances, but also the bases have therapeutic functions due to their osmotic activity.

When creating a new drug for external use, it is necessary to take into account biopharmaceutical factors that affect the therapeutic efficacy of the drug.

Pharmaceutical factors (path of administration of drugs, type of dosage form, physical and chemical state of active substances, excipients, manufacturing technology) determine the effectiveness and safety of drugs and are the basis of pharmaceutical development [322, 323, 324].

The right choice of dosage form. The composition and design of the dosage form is a compromise between the stringent requirements for the dosage form and the level of development of modern technologies. The requirements for the dosage form depend on the type of disease, the location of the focus of the pathological process, the properties of the active substances, the route of administration of the drug, and the presence of additional requirements [325, 326]. To date, the range of dosage forms has not particularly expanded, but varieties with a modified release of active substances (prolonged or accelerated) have appeared. Research in the field of creating a dosage form with desired pharmacokinetic characteristics has led to the invention of drug delivery systems [327, 328]. An analysis of the types and structures of nanocarriers, as well as the classification of excipients for delivery systems according to their functional characteristics, has already been given in the works of scientists [324, 325, 329, 330].

Thus, the biopharmaceutical development of the concept of dosage form currently makes it possible to create drugs with high efficacy and safety characteristics.

Physical and chemical properties (state) of active substances. This applies to fineness, polymorphism, crystallinity, optical properties of active substances. Chemical modification of a substance significantly affects the kinetics of its absorption and release from the body [331]. To change the properties of active substances, general pharmaceutical methods are used: the formation of salts, co-crystals, hydrates, solvates, and polymorphs [332, 333].

Recently, the substances of many active substances have been marketed in the form of solid dispersions (a dispersion of a substance in a water-soluble carrier), in which polyethylene glycol, polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose, polyvinyl alcohol, etc. are used as carriers [334].

Excipients, their nature and amount affect the therapeutic activity of active substances and the physicochemical characteristics of the dosage form during their manufacture and storage [335, 336, 337].

International pharmaceutical organizations (ICH, IPEC, FDA) proposed that excipients, along with active substances, be classified as a special gradation of substances “for pharmaceutical use”, and their quality control should be carried out according to the relevant pharmacopoeial articles. [334].

Currently, more than 500 types of excipients are used in the production of medicines in the world. Most of them are included in national and international pharmacopoeias (Eur.Ph., Br.Ph., USP, JP) or national reference books (Inactive Ingredients Guide's of the FDA, Handbook of Pharmaceutical Excipients and others) [334].

The range of excipients in the technology of soft drugs is especially wide, where their significance and role as the basis are very important and diverse [338].

There are several classifications of the bases of soft dosage forms, the principle of construction of which is important for the method of their manufacture: this is the degree of affinity of the properties of active substances and bases, the possibility of dissolving active substances in the base. In accordance with this principle, all ointment bases are divided into three groups: lipophilic, hydrophilic, lipophilic-hydrophilic.

Lipophilic (hydrophobic) bases include: a) fatty bases (animal and vegetable fats – pork fat, goose fat, beef fat, almond oil, apricot, peach, sunflower, olive, etc.), hydrogenated fats (products of industrial processing of fats and vegetable oils); b) hydrocarbon bases (vaseline, paraffin, petrolatum, vaseline oil, naftalan oil, ozokerite, ceresin); c) silicone (polydimethyl silicone fluid, polydiethyl silicone fluid, polymethylphenyl silicone fluid, aerosil, esilon – 4, 5, esilon – aerosil base).

A common disadvantage of fatty and hydrocarbon bases is the slight rancidity in air, especially in the presence of water. The pharmacological indifference of fats is directly dependent on their freshness; rancid fats irritate the skin and mucous membranes. In addition, fatty bases have an unpleasant odor and staining properties, reduce the rate of release of active substances, are subject to microbial contamination, are deficient food products and are unsuitable for the preparation of ointments containing alkalis, oxides and salts of heavy metals.

Hydrophobic bases are guaranteed to provide the form of soft drugs, but minimize the dynamic processes associated with diffusion and release of active substances, resulting in drugs that are ineffective [338]. When using hydrophobic bases, drug developers must increase the effectiveness of drugs by increasing the concentration of active substances. In addition, such bases interfere with the normal functioning of the skin, and in some cases, the use of ointments on vaseline bases is categorically contraindicated.

Hydrophilic bases include: a) gels of high molecular weight carbohydrates and proteins (soap-glycerin, starch-glycerin, gelatin-glycerin, methylcellulose, sodium carboxymethylcellulose (Na-CMC); b) synthetic (polyethylene oxide bases, polyethylene gels; c) gels of inorganic substances (concrete clay, aerosil); d) phytosterol gels.

Lipophilic-hydrophilic bases: a) absorption (alloys of lipophilic bases with emulsifiers (lanolin b / w, spermaceti, wax); b) emulsion (type m / w, w / m). However, this classification does not fully reflect modern ideas about excipients, since the same compound can be used in different dosage forms [339].

Another classification divides excipients depending on the effect on the physicochemical characteristics and pharmacokinetics of the dosage form into the following groups: formative, stabilizing, prolonging, solubilizing, corrective.

But some authors exclude the group of shaping substances, since shaping, as a rule, is the result of the combined action of several auxiliary substances with different technological functions [334].

Polymers are of great importance for the creation of new soft dosage forms. Polymers are used as fat-free bases and to stabilize emulsions and suspensions. The main polymers intended for this purpose are polyethylene oxide (PEO), polyvinyl alcohol, and PVP [339, 340, 341].

Promising are polymeric compounds whose molecules contain several types of monomer units or so-called copolymers [342, 343].

Polylactic and polyglycolic acids, as well as polymers and copolymers based on lactic and glycolic acids, are the most commonly used polymers for the creation of systems for the delivery of active substances with a prolonged action [344].

As a result of research in the field of polymers for prolongation, a number of new promising polymers have been proposed that have a high affinity for biological tissues of living organisms and, in some cases, undergo biodegradation not to free acids, but to alcohols and other, less aggressive towards biological systems, monomers. Biodegradable polyalkyl carbonates, such as polyethylene carbonate, polypropylene carbonate, copolymers of ethylene and propylene carbonates, are used as the basis for local anesthetics [345].

Polyanhydrides have great potential as biologically compatible carriers of active substances [346]. The products of biodegradation of polyanhydrides are the corresponding dicarboxylic acids, which are involved in metabolic processes. As a result of the destruction of the modified polyanhydrides, modifier residues (for example, amino acids) are additionally formed, which are chosen so that they are absorbed by the body. In this regard, polyanhydrides are of interest – esters that can undergo degradation with the formation of salicylic acid, which has anti-inflammatory properties [347].

Of considerable interest are polymer complexes, in particular, polyionic ones, which are formed by mixing oppositely charged polyelectrolytes in a solution [347]. A directed change in the conditions for obtaining such complexes (type and concentration of polymers, ratio of charged fragments of a polycation and polyanion, temperature, etc.) makes it possible to obtain nanoparticles of various types (nanoparticles, micelles, nanogels, hollow nanospheres) [347, 348, 349]. An example is polyionic complexes

based on poly-γ-glutamic acid and chitosan used to obtain nanoparticles, hydrogels, and films for biomedical applications [350].

For practical pharmacy, Ukrainian scientists provide generalized information on the properties of frequently used emulsifying substances based on the International Pharmacopoeia, which can be used to purposefully select excipients, taking into account the biomedical requirements for the drug being developed [351].

Polyethylene glycol-400, emulsifier No. 1, PEO, PVP-3, castor oil, glycerin, methylcellulose derivatives are used as thickeners, structure-forming and softening agents [352].

In modern pharmacy, microcrystalline cellulose is widely used, taking into account its ability to be dispersed under the influence of high shear stresses in water with the formation of stable gel-like dispersions [353, 354]. The high chemical purity and physiological inertness of cellulose, combined with chemical resistance, insolubility in water and organic solvents, lack of taste, odor, and color, make it possible to use it as a filler, stabilizer, and emulsifier in the pharmaceutical and cosmetic industries [355].

Currently, an intensive search for new excipients is underway in order to increase the shelf life of drugs. The addition of various stabilizing substances ensures the high efficiency of drugs for a long time, which is not only of great medical but also economic importance, since it allows to increase their shelf life [356].

The most promising in this regard is the creation of multicomponent compositions using polyethylene glycol, PVP, cellulose derivatives, and collagen as basic substances. Collagen can be obtained in the form of fibers, films, sponges, powders and gels of various viscosities. Unlike other base-forming and polymeric substances, it is water- and gas-permeable, has a high sorption capacity with respect to biologically active substances, is indifferent as a biopolymer has a high affinity for the human body, is easily resorbed and utilized in it [356].

Today, the industry produces not only a significant range, but also lines of one type of excipients, the grades of which differ in particle size, bulk density, flowability, which allows you to choose a product that provides the specified technological quality

parameters, while paying attention to particle morphology and size. Already in some countries, a classification of particles has been compiled, linking the shape and relief of their surface with technological characteristics [357, 358].

Hydrogels based on lightly cross-linked acrylic polymers are recognized as promising for the development of new bases for soft dosage forms. When applied to the skin, such gels form the thinnest smooth films, providing a prolonged effect of drugs, more fully and evenly release active substances, are well distributed over the mucous and skin surfaces, have a cooling effect, do not have toxicity and irritating effects. Applications of hydrogel-based preparations are aesthetic in appearance, do not spread, do not stain clothes, and are easily washed off with water.

Poloxamer gels are used because of their unique property, such as in situ thermoset gelling of substances. Poloxamers are well known as nonionic surfactants (surfactants) that form aqueous gels that undergo transformations from a low viscosity state to a high viscosity state as a result of an increase in temperature (thermal gelation) [359].

Romanian researchers have shown advantages of Lutrol F 127 poloxamer over Carbopol 980 and Ultrez 10 for gelling [360].

In modern dermatology, for the treatment of hyperkeratosis, hydroxy acids - alpha-hydroxy-, beta-hydroxy-, polyhydroxy acids, as well as the so-called bionic acids, are widely used, since they have not only an exfoliating effect, but also a specific activity. Alpha hydroxy acids: glycolic acid stimulates the cells of the epidermis and dermis, lactic acid has a moisturizing effect, malic acid stimulates cell metabolism, tartaric acid whitens and moisturizes well, citric acid has an antioxidant and antibacterial effect, almond acid has a pronounced antibacterial effect. Salicylic acid (beta-hydroxy acids) has keratolytic, antiseptic and anti-inflammatory properties, also inhibits sweat and sebum secretion, increases skin permeability. Of the polyhydroxy acids, gluconoloctone is increasingly used, which helps to strengthen the epidermal barrier and moisturize the skin, which has an antioxidant effect. Bionic acids include lactobionic, maltobionic, and cellobionic acids. They are extremely hygroscopic compounds; they form a transparent gel in an aqueous medium [361, 362, 363].

Modern macromolecular compounds (HMCs) (cremophor RH-40, SSMA, Lutrol F-68) increase the adsorption activity of drugs.

Pharmaceutical technology. Increasing the solubility of active substances in solvents implies a significant increase in their effectiveness. Therefore, an important issue in pharmaceutical technology is to increase the solubility of sparingly soluble active substances in water and lipids, since their bioavailability largely depends on the particle size and degree of coagulation. The smaller the particle radius, the lower the adsorption energy, which expresses the strength of the particle fixation on the interfacial surface. Therefore, too small particles are not fixed on the surface. It has been experimentally shown that particles smaller than 100 nm in size are fixed on the surface of the w/o only in an aggregated form [364]. The relationship between particle aggregation and emulsion stability is explained by the increased rheological characteristics of interfacial films.

Particle sizes affect not only the transport function and specificity of active substances, but also the rate of their excretion from the body, all other things being equal [365].

The solubility of active substances can also be increased through the use of cosolvents (benzyl benzoate, benzyl alcohol, propylene glycol (PG), PEO, etc.), hydrotropic agents (urea, sodium salicylate, etc.), as well as the phenomenon of solubilization and complex formation [366].

To increase the bioavailability of sparingly soluble active substances, Indian scientists use a promising high-pressure homogenization technique to obtain nanosuspensions. Nanosuspensions consist of pure API, sparingly soluble in water, without matrix material, suspended in a dispersion [367].

In order to increase the dissolution of albendazole, researchers at the Egyptian University used the spray drying technique, the binary mixture method with Kollicoat IR and PVP [368].

Polish scientists showed that the system of solid dispersion of clotrimazole with Pluronic F127 in a ratio of 60 : 40, developed by them and obtained by dispersion, increases the rate of dissolution of active substances [369].

The most important problem in pharmaceutical technology is the stabilization of drugs. This is due to the fact that active substances under the influence of chemical (hydrolysis, saponification, oxidation, polymerization, etc.), physical (evaporation, change in consistency, delamination, coarsening of particles) and biological (souring, etc.) phenomena change their properties. For this purpose, various chemical (adding stabilizers, antioxidants, preservatives, etc.) or physical (use of non-aqueous solvents, etc.) methods are widely used to stabilize homogeneous soft drugs. To stabilize heterogeneous drug systems (suspensions, emulsions), thickeners and emulsifiers in the form of surfactants and HMCs are used [369].

Promising for obtaining emulsion bases in the production of soft drugs are modern silicone emulsifiers – Dow Corning elastomers, which have already crossed the border of the concept of excipients due to moisturizing, softening and other properties [368].

Also, fine powders are used to stabilize disperse systems (emulsions), this is due to physicochemical properties and phenomena (absorption energy, capillary pressure, steric and electrostatic repulsion between layers, elasticity of the network-structure formed by solid particles) [370-373].

On the other hand, for easily soluble and adsorbable drugs, the problem of prolonging the release time and reducing peak concentrations remains a difficult task, for which various methods have been developed (creating containers, chemical modification, etc.).

Today, foreign scientists are actively using advanced technologies for creating nanoemulsions using various excipients. Using ultrasound, nanoemulsions of lauric acid are produced with an oil droplet size of about 100 nm. The high-pressure jet technique is also used to create coconut oil nanoemulsions [373].

Thus, the development of physics, chemistry, biochemistry determines the rapid development in the field of pharmacy. By varying various combinations of excipients, it is possible to regulate the strength and duration of the therapeutic effect of soft drugs, regulate the bioavailability of active substances, influence their accumulation in tissues and the elimination process. The main trend in the development of the production of

soft dosage forms is associated with the use of more and more effective active substances, modern excipients and the creation on their basis of combined preparations intended for the treatment of certain diseases, taking into account their etiology and pathogenesis.