4.4 Substantiation of general methodology of pharmaceutical development of local medicine for treatment of wounds

The problem of wound healing is one of the most pressing problems of our time [239-241]. According to the literature, purulent-necrotic soft tissue diseases occupy one of the leading places among surgical diseases: surgical patients with purulent-inflammatory diseases are 35-45%, and postoperative purulent complications occur in 24-30% of cases [241-246]. The armed conflict in eastern Ukraine (2014) and hostilities on the territory of Ukraine (2022) led to the actualization of combat surgical trauma, both for the military and the national health care system.

According to Ya.L. Zarutsky, IP Khomenko and co-authors, in modern local military conflicts the frequency of isolated wounds reaches 60-65%, multiple - 10-13%, combined - 20-22%, combined - 2-3%. A significant part (up to 60%) are explosive injuries [247, 248].

Wounds - mechanical damage to the integrity of the skin or mucous membranes. They are among the most common injuries in both wartime and peacetime. A gunshot wound is damage to tissues and organs in violation of the integrity of their cover - skin, mucous membranes or serous membranes, caused by firearms, and is characterized by a zone of primary necrosis and changes in surrounding tissues that cause foci of secondary necrosis and primary microbial [248].

There are different classifications of wounds: by nature, by cause of injury, by anatomical location, by type of microflora, etc. (Table. 1).

Table 1

Classification of surgical infections of the skin and soft tissues (according to Saveliev VS) [249].

The nature of the infection	Classification by severity	The level of damage	Disease	The International Statistical Classification of Diseases and Related Health Problems. 10th revision (ICD-10)
Primary	Uncomplicated infections	1 level - skin	- boil, furunculosis; - they were	L02 A46
		Level 2 - subcutaneous tissue	- carbuncle; - hydradenitis; - uncomplicated abscesses; - cellulite; - Phlegmon	L02 L73.2 L02 L08 L03
	Complicated infections	Level 1 - subcutaneous tissue	- necrotic cellulite	M79
		Level 3 - superficial fascia	- necrotic fasciitis	M72.5
		Level 4 - muscles and deep fascial structures	- pyomyositis; - myonecrosis	M60 A48

Secondary	Complicated infections	1-4 levels of damage	- bites; - postoperative wounds; - diabetic foot syndrome; - trophic ulcers; - bedsores; - burns	W53-W59 T80-88 E10.5, E11.5 183.0,183.2 L89 T30

Classification of gunshot wounds, developed by Ya.L. Zarutsky and co-authors, provides for the division into groups [248]:

1. 1. in size: small (up to 2 cm in diameter); medium (from 2 to 10 cm); large (10 to 20 cm); extra large (over 20 cm);
2. 2. in the form of a wound canal: slit-like; cylindrical; funnel-shaped; with the shape of a truncated cone; diamond-shaped; complex;
3. 3. in the direction of the wound canal: linear; nonlinear;
4. 4. by area of lesion: small (up to 2 cm^2); medium (from 2 to 50 cm^2); large (from 50 to 200 cm^2); extra large (over 200 cm2);
5. 5. by the volume of the lesion: small (up to 2 cm3); medium (from 2 to 125 cm^3); large (from 125 to 1000 cm^3); extra large (over 1000 cm^3).

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 [250-255]. 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 [255, 256].

The scientific literature presents a significant number of classifications of the wound process, specialists most often used classifications MI Kuzina, BM Datsenko and D. Krasner [255- 258].

D. Krasner proposed a classification of the wound process BYRP (BlackYellowRedPink), which contains four stages [258]. According to this system, different colors correspond to different phases of the wound process: B (Black) black - necrosis, Y (Yellow) yellow - fibrin in the wound, R (Red) red - granulation tissue, P (Pink) pink - wound epithelization. The graphic scheme accurately reproduces the clinical picture of the color change of the wound depending on the processes occurring in it. In this case, stages B and Y correspond to the first phase of the wound process according to MI Cousins, and stages R and P correspond to phases II and III [259].

Combat injury - a special type of injury, which differs from domestic or industrial not only the damaging factor, but also the conditions of injury, the timing of assistance to the victim, the mass of injuries. Data on the treatment of this pathology are poorly covered in the literature, in addition, they are rapidly becoming obsolete due to the continuous improvement of weapons and medical technology. Currently, the development and implementation of modern principles of combat trauma treatment in Ukraine is an urgent task.

Combat injuries include gunshot and non-gunshot wounds, as well as injuries due to exposure to various types of weapons of mass destruction.

A gunshot wound should be considered a severe violation of vital functions of the body, directly dependent on the nature of the damage and general regulatory disorders. An obligatory component of a gunshot wound is its microbial contamination. Therefore, in case of gunshot wounds, it is advisable not to talk about antibiotic prophylaxis, but about antibiotic therapy of a known existing infection.

According to the US Center for Excellence in Disaster Management and Humanitarian Aid, mortality from delayed injuries such as infection reaches 12% of total mortality from combat trauma, second only to severe central nervous system (CNS) damage and non-life-threatening thoracic injuries. , death from which occurs directly on the battlefield. This emphasizes once again that the fight against wound infection is one of the priorities in the treatment of gunshot wounds.

A gunshot wound differs from wounds of other origins (stabbed, cut, chopped, etc.) by the following features:

- the presence of a zone of necrotic tissue around the wound canal (primary necrosis);

- the formation of new foci of necrosis in the next hours and days after injury (secondary necrosis);

- uneven length of damaged and dead tissue outside the wound canal, due to the complexity of its architecture (primary and secondary deviations);

- frequent presence in the tissues surrounding the wound canal of MS and other foreign bodies.

Infectious complications in modern military conflicts, according to JL Zarutsky and co-authors, occur in 25-35% of the wounded [242, 248]. A gunshot wound always contains mixed microbial flora, as well as necrotic tissue, which is a favorable environment for the development of the infectious process. Multiple shrapnel wounds and explosive injuries pose a special threat to the development of infectious complications of wounds [260 - 262].

The level of microbial contamination of the wound has a decisive influence on the development of wound infection - if the critical level of microorganisms is exceeded (10^5-10^6 per 1 g of wound tissue), the probability of developing wound infection increases significantly. Etiological factors of infectious complications of combat trauma there are representatives of gram-positive, gram-negative and non-clostridial anaerobic flora [242, 248]. Almost 80% of wound infectious complications by etiology are mixed - aerobic-anaerobic, but microbial associations in different conditions can cause a process with a predominance of purulent (aerobic) or putrefactive (anaerobic) inflammation [248, 261]. In the process of treatment, the microbiological spectrum of gunshot wounds is constantly changing - the "primary" microbial association is joined by hospital strains, and under the influence of local and antibacterial therapy there is a selection of "stable" opportunistic nosocomial bacterial strains with fungal infection [242, 248, 261].

In the case of a purulent wound, inflammation is combined with the processes of formation of a purulent lesion, which are caused by the penetration and reproduction of pathogenic purulent microorganisms [239, 241, 263-265]. According to many

experts, recently under the influence of various factors, the main of which there is a selective action of antibiotics, there have been significant changes in the etiology of wound infections [239, 240, 242, 243]. Currently, the main pathogens are: staphylococci (S. Aureus, S. epidermidis); hemolytic and non-hemolytic streptococci; members of the family Enterobacteriaceae (E. Coli, Citrobactersspp., Klebsiellaspp., Enterobacterspp., Serratiaspp., Proteusspp., Proteusspp., Providenciaspp.); non-fermenting gram-negative bacteria (Pseudomonasspp., Acinetobacterspp., Moraxellaspp., Flavobacterium, Achromobacter); obligate anaerobic microorganisms that do not form spores (Bacteroides, Fusobacterium, Peptococcus, Peptostreptococcus) [243, 272].

LA Blatun was determined that in the group with acute purulent diseases in 69.5% of cases staphylococcus is detected in monoculture, at the same time in the case of post-traumatic purulent wounds or chronic purulent diseases of the skin and soft tissues, associations of pathogenic microorganisms are determined [267 , 268]. There was also an increase in the incidence of fungal infections - up to 9.9% [268].

VK Gostishchev recorded the presence of staphylococcus in monoculture in 68.7% of cases of purulent diseases of various localizations, as well as in association with Escherichia coli - in 9.3%, streptococci - in 0.4%, proteus - 0.2% of cases [239]. Escherichia coli in its pure form and various associations were found in 14.5% of cases, streptococcus - in 2.8%, proteus - in 0.7%, fungi - in 0.1% of cases [239].

The species composition of microorganisms removed from purulent wounds differs significantly in different clinical groups. Thus, in patients with open fractures of long tubular bones and suppuration of wounds, gram-negative microflora predominates (75.4%). In 83.3% of patients with acute purulent wound diseases, gram-positive bacteria in monoculture were identified, and in 16.7% - associations of gram-positive and gram-negative bacteria; in chronic diseases of the skin and soft tissues, these figures were 60.0% and 40.0%, respectively [269, 270].

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:

- rapid wound cleansing;

- suppression of wound microflora;

- reduction of inflammatory-infiltrative processes in the wound;

- acceleration of reparative processes [239-241, 243, 244, 246].

The evolution of ideas about wound healing has gone through 3 stages, which did not deny, but complemented the previous ones:

1) the theory of wet wound healing (1962) - proved the benefits of wound healing in a humid environment compared to dry dressings, reducing the role of MLZ on lipophilic bases [256, 271, 272];

2) differentiated approach to treatment (1992) - treatment according to the etiology and stage of the wound process, which led to the development of modern dressings and Soft medicines on hydrophilic bases [251, 253, 273, 274];

3) the theory of treatment of the wound base "Woundbedpreparation" (2000) - the need to translate a chronic wound into acute [275, 276].

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 [244, 276-279], 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 [241, 243, 244, 246].

The leading role in the complex treatment of purulent wounds of any genesis belongs to the surgical treatment of the wound, and, according to VV Privolnev. with co-authors, exudation is significantly reduced, time to epithelialization and total treatment time is reduced, the risk of infectious complications is reduced [279]. Debridement can be surgical, mechanical, physical, chemical or biological [239, 280].

Methods of local treatment of wounds are divided into two groups:

1) open method - can be implemented by treatment under a bandage or non-bandage method in a controlled abacterial environment;

2) closed method - the imposition of the primary seam in conditions of adequate drainage [240, 244].

Ensuring the obligatory principle of wound healing - maintaining a moist environment in the wound - is achieved by modern dressings for different phases of the wound process [279- 284], drugs for topical use on hydrophilic bases [243, 244, 277-285], VAC-therapy [243, 279, 280, 286], flow-flushing wound drainage and physical therapies [243, 244, 248, 287, 288].

The general scheme of treatment of purulent wounds, proposed by S.Ya. Ivanus and P.N. Zubarev and co-authors (2017) [289], shown in Fig. 1.

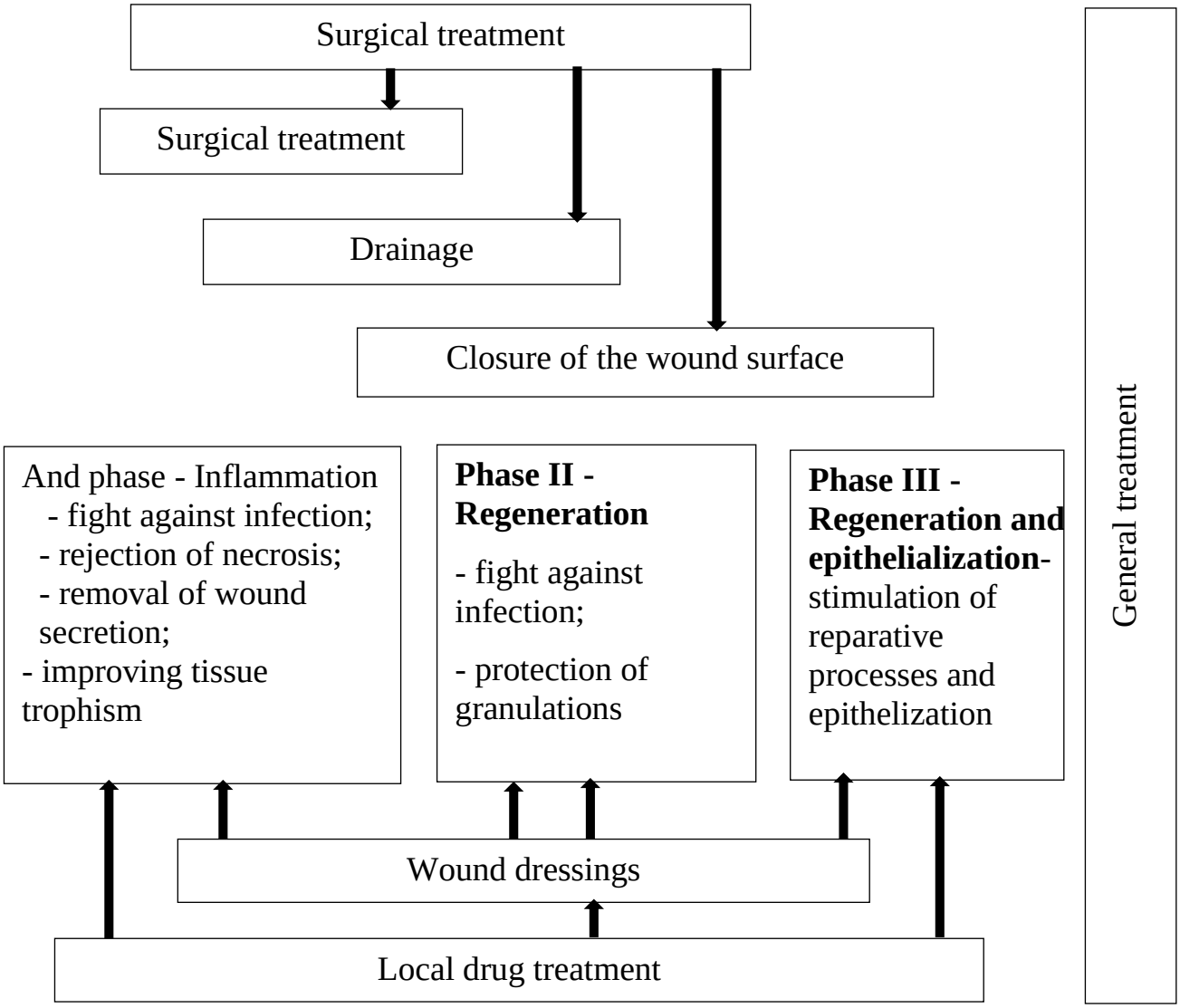

Figure 1 - General scheme of treatment of purulent wounds [289]

Important for the influence on the leading factors of pathogenesis are drugs for topical use - antiseptics and antibacterial agents, enzyme preparations, sorbents, agents that promote repair and epithelialization [239-241, 243, 244, 246, 287, 288].

Antiseptic solutions that accelerate the elimination of infection, prevent secondary infection and increase the effectiveness of debridement, have long been used and continue to be actively used in phases I and II of the wound process [243, 284, 296]. When choosing antiseptics, preference is given to drugs with a broad spectrum of action that are active against mixed microflora [239-241, 243, 279].

Optimal antiseptics for local treatment of purulent wounds

currently there are: 0.35-4% solutions of povidone-iodine [279, 290-292], 0.01% solution of miramistin [307], 0.02-0.05% solutions of chlorhexidine [290, 292], polyhexanide , combinations of octenidine dihydrochloride with phenoxyethanol [290, 290, 293]. An important feature of modern antiseptics from the group of cationic surfactants (surfactants) is the ability to facilitate the removal of microbial biofilms, which are formed during prolonged stay in the wound of microorganisms and fungi, and provide pathogens with protection from UV radiation, phagocytosis, [268, 289].

A number of authors note the effectiveness of neutral anolyte, which detects antibacterial, anti-edematous, anti-inflammatory and detoxifying effect [270, 278, 294].

In the treatment of wounds in the third phase of the wound process, antiseptic solutions can be used only to treat the skin around the wound to prevent secondary infection [241, 243, 279].

However, antiseptic solutions have certain disadvantages. Thus, a solution of hydrogen peroxide 3%, simultaneously with the ability to quickly remove purulent-necrotic masses from the wound and bactericidal effect against anaerobic bacteria, has a cytotoxic effect on granulation tissue and fibroblasts [243, 279].

The use of alcoholic solutions of antiseptics is inappropriate because they cause burns of immature granulations and pain [279, 295]. It is also undesirable to use antiseptic dyes, due to their cytotoxicity and stable staining of tissues, which complicates the analysis of the situation in the wound. Potassium permanganate

solution causes drying of the epidermis, even to necrosis [279], and furacillin solution has low antimicrobial activity [284].

A number of studies have confirmed the reduction of side effects of antiseptic drugs while maintaining therapeutic efficacy as a part of soft medicines - ointments, creams, gels, namely: ointments, creams and liposomal hydrogel with the content of povidone-iodine [291, 296-299], ointments with dioksidinom [279, 314, 315], creams and ointments with silver sulfadiazine [279, 298], ointments with miramistin [279, 298, 299], gels with hydrogen peroxide [298] and chlorhexidine [299].

An alternative to antiseptics is the systemic or topical use of antibiotics. It is well known that the beginning of antibacterial therapy more than 2 hours before surgery reduces the likelihood of postoperative infection to 3.8% of cases compared with 8.5% of cases with antibiotics 1 hour before surgery [240, 270, 300, 301]. Most often in surgical practice, penicillins (38.5%), aminoglycosides (15.7%), fluoroquinolones (12.5%), cephalosporins (10.3%) are prescribed, and in case of signs of non-clostridial aerobic infection - combined antibacterial therapy (16, 3%) [239, 240, 243, 270, 302].

However, systemic antibiotic therapy is often associated with parenteral deficiencies, treatment of adverse events and history of allergies, so the widespread use of topical antibiotics [303].

Specialists have identified the following benefits of topical antibiotics:

- high concentration of antibiotic at the site of surgical infection;
- minimal systemic antibacterial action and systemic toxicity;
- reducing the risk of antibiotic resistance in the absence of concomitant systemic therapy with antibiotics;
- additional impact on the wound process when using combined drugs;
- ease of use [299-302].

The disadvantages of topical antibiotics are:

- limited number of effective antibiotics for topical use;
- weak penetration of the antibiotic into the tissues;
- the possibility of a systemic effect when applying an antibiotic on a significant area of the wound;

- possible hypersensitivity and allergic manifestations;

- the potential for slowing down tissue regeneration when using topical agents;

- the complexity of accurate dosing;

- the possibility of contamination of the contents of the container with prolonged use of drugs [286 - 289].

In the last century, the development of a new antibacterial agent for the local treatment of infection was the simple introduction of effective antibiotics to the ointment base, which led to the development of tetracycline, erythromycin, doxycycline ointment and lipomphilic syntomycin liniment [280]. indications for use [306]. The beginning of the development of ointments with antibiotics on osmotically active hydrophilic bases allowed to provide a differentiated approach to treatment taking into account the stage of the wound process [279, 306]. According to experts, at the present stage it is advisable to use ointments with antibiotics bacitracin, mupirocin, fusidic acid, neomycin, retapamulin, chloramphenicol, erythromycin and ofloxacin, which are active against staphylococci, streptococci, corynebacteria and clonebacteria. does not decrease with bleeding, accumulation of exudate, necrosis [279, 295, 304, 306]. The effectiveness of combining the antibiotics bacitracin and neomycin, between which there is a synergism [279, 306], has been confirmed.

In the first phase of the wound process can also be used drugs based on bacteriophages, which are characterized by highly selective bactericidal action and the ability to destroy biofilms [307].

Proteolytic enzymes (trypsin, chymotrypsin), bacterial enzymes (streptokinase, collagenase) and others can be used to clean the wound surface from non-viable tissues. [243, 308]. However, experience with monoenzyme therapy has shown its low effectiveness, because in a purulent wound, due to acidosis, most enzymes quickly lose their activity, in addition, after lysis of necrotic tissues, the manifestations of poisoning by decay products increase [308].

As a rule, purulent wounds produce a significant amount of exudate, which requires its removal from the wound surface to prevent the absorption of tissue

destruction products into the bloodstream. This fact determines the possibility of using sorbents in the treatment of purulent wounds [283, 308].

Some authors have recommended the local use of recombinant cytokines, which have the ability to regulate the wound process at all stages - from increased migration and functional activity of neutrophils, which leads to a decrease in microbial contamination of the wound and its cleaning in the early stages - to the activation of fibroblastic processes in the later stages [309, 310].

Attempts to simultaneously influence several factors of pathogenesis led to the development of complex drugs for certain phases of the wound process. Thus, for the first phase the expediency of using combinations of antibacterial agents (batracin and neomycin; benzalkonium chloride and metronidazole) and their combination with proteolytic enzymes (ultralysine and miramistin; clostridiopeptidase and chloramphenicol) was proved; in the first and second phases it is recommended to use antiseptics and agents that promote tissue repair (silver sulfadiazine and epidermal recombinant human growth factor; benzalkonium chloride, chloramphenicol and dexpanthenol; ethonium, thiotriazoline and lidocaine hydrochloride); for the second phase of the wound process, the effectiveness of an antibacterial agent in combination with an anesthetic and a substance that accelerates epithelization (chloramphenicol with methyluracil or chloramphenicol with trimecaine and methyluracil) has been shown [312-314].

The expediency of the introduction of drugs for the treatment of infected and purulent wounds local anesthetics due to their ability not only to reduce pain during inflammation, but also proven by numerous studies "in vitro" and "in vivo" antimicrobial activity in topical applications against staphylococci, streptococci, intestinal rods and other microorganisms [315].

In order to influence the processes of tissue regeneration in phases II and III of the wound process, the combined drugs include drugs with anabolic and anticatabolic activity, which have anti-inflammatory action, ability to accelerate wound healing, stimulate cellular and humoral protective factors, among which exclusively methyluracil [316]. However, recent studies have shown the use of thiotriazoline [317,

318], dexpanthenol [313], pyrimidine nucleoside analogue ximedon [319], a combination of zinc salt of hyaluronic acid and thiotriazoline [320].

Thus, it is significant that the main approaches at the present stage are the pathogenetic orientation in accordance with the phase of the wound process and the complex effect on the leading factors of pathogenesis. concentration of active ingredients in the affected area, providing high therapeutic efficacy and prolonged action with minimal side effects of the components.

Achieving prolonged action of the drug provide excipients. Thanks to modern excipients, it is possible to program drugs with specified pharmacokinetic properties, which is of great importance for both medicine and pharmacy. Drugs with specified pharmacokinetic properties reduce the likelihood of adverse reactions and create all the conditions for more complete absorption of active substances. In addition, they provide a therapeutic effect with small doses of active substances. The specified pharmacokinetic properties can also be created by maintaining in the composition of the base polymer solutions. The latter provide, inter alia, the prolongation of the therapeutic effect of the drug.

The range of drugs of local action registered in Ukraine is very rich and wide. But the fighting in Ukraine showed the lack of not only soft drugs, but also soft drugs of multidirectional action, corresponding to modern ideas of wound healing.

Local treatment of gunshot wounds, containing mixed microflora and necrotic tissues, is the use of antibacterial substances to control microorganisms; providing drainage of exudate; reducing the inflammatory reaction. Therefore, effective pharmacotherapy of gunshot wounds is to individualize treatment approaches and the choice of drugs and excipients.

According to the literature [321], the structure of pathogens of wound infection is represented by a mixed microflora: gram-positive cocci (staphylococci, streptococci, enterococci); gram-negative rods (Escherichia coli, Proteus, Klebsiella); anaerobic gram-positive and gram-negative rods (Clostridia, Bacteroides, Prevotella). Pseudomonas, Enterobacter, Acinetobacter, Serratia - are found in the wounded, hospitalized for a long time; Candida is observed in the wounded during long-term

hospitalization, in persons with immunosuppression or malnutrition, who were treated with antibiotics, corticosteroids [322, 323].

Given the above, the question arises: is it possible to create an ideal drug that would meet the modern requirements of pharmacotherapy of gunshot wounds. No, because the microflora changes, new resistant strains of microorganisms appear and there is no clear line between the phases of the wound. Therefore in the basis of development of soft medicines of local action we put scientific achievements of pharmacotherapy of a gunshot wound that defines a choice of structure of drugs for treatment of this pathology.

Based on the pathology of the wound, we based the development of drugs on the following requirements: antimicrobial, anti-inflammatory and wound-healing effects of the drug, prolonged effect and compliance.

The basis of the drug affects the effectiveness of the drug: prolonged release of active ingredients, creating a moist environment, providing a certain pH environment, which in turn will promote cleansing and wound healing. Therefore, when creating drugs, our main task was the choice of active ingredients, excipients and the development of the basis of the drug.

Medico-biological requirements for topical drugs include physicochemical (complete release of active ingredients, physicochemical stability, lack of irritating and sensitizing effects, compliance) and technological indicators (reproducibility of technology, minimum technological stages of production).

Given that topical drugs are intended for the treatment of wound processes, there are a number of medical and biological requirements for the drug:

- ✓ □ Release of active ingredients from the base;
- ✓ □ Lack of irritating and sensitizing effects;
- ✓ □ Storage stability;
- ✓ □ Compliance.

To the technological process:

- ✓ □ Reproducibility of technology;
- ✓ □ The technological process should be as energy-intensive as possible;

✓ □ The number of stages of production should be minimal.

The methodological basis of this work is the theory of scientific knowledge of pharmaceutical development and research of drugs with the establishment of their pharmaco-technological and physico-chemical parameters.

Methodology of pharmaceutical development of soft medicines for treatment of wound process is resulted in fig. 2.

Thus, the development of technology and the study of multidirectional drugs is relevant, as evidenced by the fighting in Ukraine.

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 application drugs are the release of active ingredients from the dosage form and penetration through biological membranes to the lesion. The release of active ingredients is the initial and very important stage of ensuring the therapeutic effect of the drug. Pharmaceutical factors are crucial at this stage: physical properties of active ingredients and excipients, nature and amount of carrier base and excipients that are part of the drug, type of dosage form and technological operations carried out in the manufacture of the drug.

Carrier bases are important components of application drugs, as they account for 90% or more of the total mass and affect the activity of active ingredients and rheological properties of the dosage form.

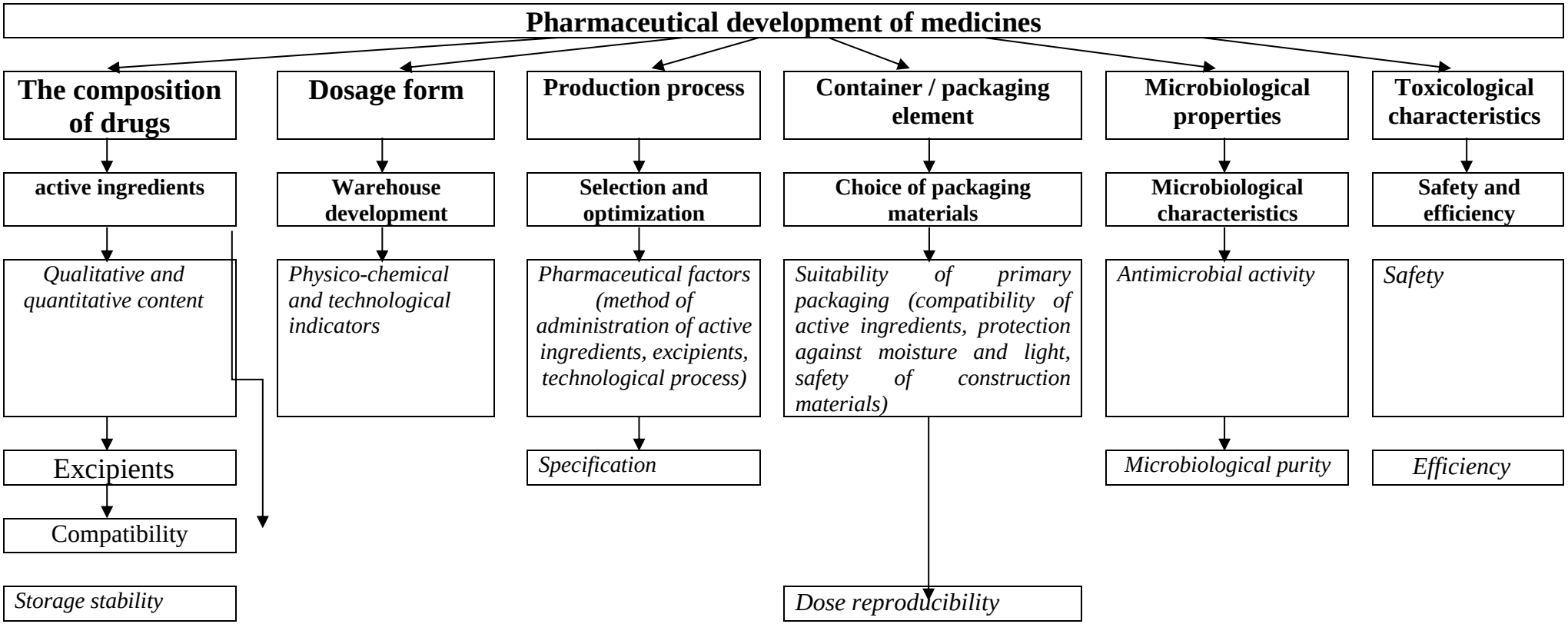

Figure 2 - Methodology of pharmaceutical drug development