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"Nicolae Testemitanu" State University of Medicine and Pharmacy

Faculty of Pharmacy

GUIDE

regarding the practical license period

for 5th year students,

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GUIDE REGARDING THE PRACTICAL LICENCE PERIOD FOR 5th YEAR STUDENTS, FACULTY OF PHARMACY

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CONTENT

Chapter 1.

EXERCISE OF THE PHARMACIST PROFESSION AND PHARMACEUTICAL ACTIVITY. ORGANIZATION OF THE PHARMACEUTICAL ACTIVITY.

Authors: **Mihail Brumarel, Stela Adauji**

The social orientation of the pharmaceutical service leaves its mark on the pharmacist's role in the health system. The importance of this problem has become more current and acute, as the market economy conditions are increasingly disregarding the role of the pharmacist, reaching up to the equalization between pharmacist and trader.

Updating the pharmacist's role in contemporary society was initiated at the session of the World Health Organization in Tokyo, 1993 with the generic "The role of the pharmacist in the health system In the WHO report for this international forum it is mentioned that effective medicine can only be practiced under conditions of effective drug management". This axiom applies equally to developed and developing countries. Only if the pharmacist is accepted as a vital partner of the healthcare team, healthcare services with a required level of professionalism can be organized.

WHO points out that the pharmacist, as a partner of the health team, through his own high-level and multidisciplinary scientific training is the only qualified specialist, whose competence has already been approved in:

- ✓ *management and administration of pharmaceutical services;*
- ✓ *elaboration of legislation in the field of medicine and monitoring of their application;*
- ✓ *pharmaceutical formulation and quality control of their products;*
- ✓ *inspection and evaluation of drug production units;*
- ✓ *the process of registration of medicines in order to certify their quality, efficacy and safety;*
- ✓ *ensuring the quality of pharmaceutical products throughout their circulation;*
- ✓ *purchase of medicines;*
- ✓ *the activity of national institutionalized committees of profile.*

The training and specialized knowledge of the pharmacist in the field of medicine determines his involvement in the following fields of activity:

1. Administration and management of the drug.

The WHO report highlights the important role of the pharmacist in administration, insisting on the position that the pharmaceutical coordination subsystem has in the health system. Pharmacists working in the administration, are directly involved in formulating and implementing the drug policy, are responsible for the pharmaceutical management, which includes the selection of essential drugs, quality assurance of the drug, procurement, distribution and rational use thereof.

2. Community pharmacy (public).

The community pharmacist is, among the health professionals, the most accessible to the publicIf the doctor is the specialist in the field of diagnosis and treatment, the pharmacist is the specialist in the field of medicine. Their skills are complementary and only by working together can provide the necessary services to the public.

If, by tradition, the pharmacist had the role of drug preparation, in the last 20 years we have witnessed an evolution and at the same time a practically total modification of this role, the pharmacist becoming more and more a pharmacotherapist, who is able to provide all the information and the necessary consultations with the patient regarding the medicine, prescribed or not prescribed by the doctor. In this direction, the role of the pharmacist will increase in the future. WHO points out that the most important activities of the community pharmacist are:

2.1. Dispensing of prescription drugs (prescription). The pharmacist verifies the legality, safety and correctness of the prescription. There are European countries where the pharmacist holds records of patients in whom treatment has been received previously, the history of current medication and, as a result, he can provide information and consultations to the doctor to determine the treatment.

The pharmacist is the one who clarifies the medical prescription: it is statistically demonstrated that the patient does not remember during his visit to the doctor only a small part of the information provided about the medicine, his interest being focused on the diagnosis that is given to him. The pharmacist is the one who translates into a secular language, as understood by each patient, the medical prescription, which must ensure that the information provided is fully memorized by the patient and is as individualized as possible in relation to age, sex, physiological status. of the patient (child, pregnant woman, old woman), the stage of the disease, the medication used previously, makes clear indications regarding the doses, the schedule of administration and the duration of treatment; the pharmacist also informs the patient about the hygiene measures to follow, the diet and the way of life to follow, about storing the medicines in domestic conditions. Keeping in mind that verbal information through pharmacist-patient dialogue is essential, in some European countries it is tried to optimize it by providing written information on self-adhesive labels that are applied directly to the prepared form.**.** In most countries, patients show great confidence in the pharmacist's knowledge and take into account pharmacist's recommendations.

2.2. Dispensing of medicines without a prescription. The continuous increase of the health costs has forced the responsible authorities of all countries to resort to different ways to achieve savings. One of the most important is the passing of the responsibility of health, when possible, on behalf of the individual. Self-medication is today an essential, well-defined aspect of the health system. Self-medication is the patient's use of non-prescription medicines, on his own initiative, on his own responsibility, based on the recommendations of the pharmacist or other healthcare worker. Guvernele, profesioniştii din domeniul sănătăţii şi grupurile de consumatori recunosc importanţa medicamentelor fără prescripţie în cadrul sistemului de sănătate. On the other hand, consumers themselves are expressing their desire to take responsibility for their own health. The doctor consults when the patient is concerned about the manifestations of a disease or the action of a particular drug. In the case of minor disorders, he wants to be able to take care of himself, without calling for a medical consultation..

2.3. Monitoring of drug use. In the 3rd position among the duties of the community pharmacist after the distribution of medicines with or without prescription, WHO places the monitoring of the drug use. This refers, first and foremost, to drug use, but also to other programs that the pharmacist can and should be a part of. One of the most important issues is analyzing prescriptions for monitoring adverse reactions. In some Western European countries, voluntary drug monitoring programs are created, in which the pharmacist plays a specific role, in his dual role as an investigator of adverse reactions among consumers - patients and information providers. Such programs require close collaboration with the physician and can play an important role in optimizing pharmacotherapy..

2.4. Ex tempore preparation and small scale manufacture (in stock) of medicines. Given that the extraordinary development of the pharmaceutical industry allows all the substances of therapeutic interest to be conditioned in the most diverse pharmaceutical forms and concentrations, there is a significant reduction of the magisterial prescriptions worldwide and consequently a reduction of the galenic practice in the pharmacy.

However, magisterial preparation of medicines still has reason to exist and the arguments that support this claim are:

- ✓ professional, because the pharmacist is the only specialist with university studies who benefit from a complex galenic formation and it is absolutely necessary to keep this specific know-how in the possession of pharmacists, as qualified specialists to evaluate the production methods to solve the problems regarding incompatibilities, ensuring stability and others;
- ✓ therapeutic, because the magisterial prescriptions represent the will and the therapeutic choice of the doctor, and the possibility of individualizing the therapy requires the development of the galenic office practice;
- ✓ economic, because in many European countries, magisterial prescriptions are reimbursable through the social insurance system, medicines prepared ex tempore are cheaper;
- ✓ legal, because most health laws in all countries give the pharmacist the right to prepare and distribute medicines in his pharmacy, under the control of the competent authorities.

2.5. Creating conditions for the exercise of alternative and traditional medicine. WHO points out that in some countries, pharmacists are developing so-called "traditional medicines" and homeopathic products.

2.6. Informing healthcare professionals and the public. The pharmacist must collect and store information on all medicines, especially those newly introduced to therapeutics, to provide this information if necessary, to other healthcare professionals and patients. The pharmacist must use this information in promoting the rational use of medicines.

2.7. Health promotion. The pharmacist can and must participate in health promotion campaigns at local and national level in a wide range of health-related issues and especially on drug-related issues (eg, rational drug use, alcohol abuse, combating smoking, discouraging drug use during pregnancy, poisoning prevention), or other topics related to the risk of illness (tuberculosis, scabies, HIV / AIDS infection) and family planning topics. The pharmacist can also take part in educating the groups in the local community in order to promote health and participate in the disease prevention campaigns..

2.8. Providing services at home. In some countries, the pharmacist provides his information and consultations to the residences of the elderly and other long-term patients; In other countries, policies have been developed in which the pharmacist visits certain categories of immobilized patients and offers advice on the necessary medication, similar to the situation in which patients may arrive at the pharmacy.

3. Hospital pharmacy, clinical pharmacy.

The hospital pharmacy, by its situation, implies the involvement of the pharmacist in the clinical sphere - a role that pharmacists from all developed countries do not delay, to bring them closer.

Most of the prerogatives of the community pharmacist can also be found in the activity of the hospital pharmacist, but there are some distinctions that WHO emphasizes regarding the role of the pharmacist.:

- ✓ *numerous and more important occasions to collaborate (to work in interaction) with the doctor and other hospital staff* to promote the prescribing and rational use of the drug, having, first and foremost, the benefit / risk ratio in the most convenient economic conditions determined by the benefit / cost ratio. The rational use of the drug means its use under normal conditions, "standard", but it also means an adapted, personalized and optimized use of the drug (by optimizing the benefit / risk ratio and the benefit / cost ratio);
- ✓ *occasion of an activity agreed with the other pharmacists in the hospital;*
- ✓ *access to patient observation sheets and all medical records:* the pharmacist can influence the selection of medicines, the doses in which they are prescribed, the routes of administration and can follow the diet;
- ✓ *the possibility of monitoring the patient's compliance and its response to the medication administered,* the pharmacist having the responsibility to recognize and report adverse reactions;
- ✓ greater possibility compared to that of the community pharmacist to *assess treatment regimens and make recommendations for change where necessary;*
- ✓ *must be a member of the board of the hospital in which its policy is established,* firstly, the one related to the drug, the use of antibiotics, the formulation of a list of the essential drugs from the respective unit (the Pharmacotherapeutic Form of the medical-sanitary institution), the prevention of the intra-hospital infections;
- ✓ *takes part in the organization and conduct of clinical trials;*
- ✓ *prepares individualized magisterial medicines (especially for parenteral nutrition, cytostatics, analgesics, dermatological preparations, AIDS treatment preparations, etc.)*.

4. In the pharmaceutical industry.

In Europe, the industrial production of the medicinal product is not accepted until after a rigorous implementation and strict supervision of the continuous observance of the Good Manufacturing Practice Rule (GMP) in the production unit. Only the observance of these rules allows the reproducibility of the manufacturing process to be ensured for a medicinal product and, implicitly, it assures its quality.

Regarding the role of the pharmacist in the industry, it should be mentioned that the pharmacist occupies, in almost all European countries, the key positions in the drug-producing industry, that is to say, he is responsible for quality assurance and often he is responsible for the production.

5. In academic activity.

WHO emphasizes that a large number of pharmacists must be part of the "academic staff" of any pharmacy faculty and they must be appropriately involved in the education and training process, in pharmaceutical practice and in research, these three aspects of the academic activity being interdependent.

As is often emphasized, a satisfactory standard of pharmaceutical education, absolutely mandatory for obtaining adequate pharmaceutical services from future graduates, can only be achieved if the educational institution has a sufficient number of teachers with the necessary qualification, possibly with studies postgraduate, with adequate equipment and bibliographic material.

6. Training of other persons working in the health field.

The pharmacist has a duty, precisely in the interest of optimizing drug treatment, to instruct the other members of the healthcare team, in particular, about the rational use of medicines, the correct storage of pharmaceuticals, the abuse of drugs, etc. In this way, the society needs the pharmacist's immediate help in the continuous elaboration and implementation of the health policy that responds to the needs and aspirations of the population.

7. Scientific research in the field of medicine and pharmaceutical activity.

The deontological code of pharmacists. Over the years, several efforts have been made to develop a code of requirements for pharmacists, on which to base the exercise of the profession in relations with the doctor, patient, colleagues, society. Thus, at the General Assembly of the International Pharmaceutical Federation, which took place in Copenhagen, on September 2, 1960, the International Code of Pharmaceutical Deontology was adopted. The code consists of rules and regulations of professional ethics, which regulate the duties and behavior of the pharmacist in his professional activity. The Code includes 4 general titles: the general duties of the pharmacist, the prohibition of certain procedures in search of clients, rules to observe in public relations, relations with members of other health professions, the main objectives of the Code being: the protection of patients' rights; compliance with professional obligations by pharmacists; defending professional dignity and prestige. The relationships between pharmacists and the beneficiaries of the services provided must be based on trust in the pharmacist's professional competence and experience.

In our country, each graduate: pharmacist or laboratory-pharmacist, before receiving the diploma of studies, takes the Professional Oath, and in the professional activity it is due to respect the norms and requirements of the Code of deontology of pharmacists of the Republic of Moldova, approved at the 2nd Meeting of the To the Pharmacists' Association of the Republic of Moldova on May 27, 1998 (box 1.1).

According to the definition presented in article 1 of the Law on the pharmaceutical activity *"The pharmaceutical activity is a scientific-practical field of health protection, which includes researches oriented towards the creation of medicinal remedies and preparations, analysis, standardization, registration, production, preparation, quality control, keeping, informing, delivering and releasing them to the population as well as the management of the pharmaceutical units and their subdivisions ".*

The first and most important generalizing feature of the pharmaceutical activity is the membership of this activity in the scientific-practical field of health protection. The classification by some legislative and normative acts of the pharmaceutical activity in fields other than the one of the health can be considered an error and a neglect of the profession of pharmacist.

Box 1.1.

The deontological code of pharmacists in the Republic of Moldova

Article 1. **General provisions**

The code of deontology of pharmacists in the Republic of Moldova includes the main norms of ethics and pharmaceutical deontology regarding the behavior of pharmacists in the process of professional activity.

This Code establishes the relationships of pharmacists in society, towards patients, medical workers, colleagues.

The deontological code reflects the particularities of the profession, is based on the traditions of universal pharmacy and includes the moral responsibilities of pharmacists. It offers to guide the ethical criteria in the professional activity and is meant to contribute to the consolidation of the pharmacist's prestige in the society, the improvement of the pharmaceutical activity in the Republic of Moldova.

Article 2. **General obligations of pharmacists in society**

(1) General obligations

The pharmacist has the obligation to provide pharmaceutical assistance to any person irrespective of nationality, race, sex, social status, religion or political beliefs.

The pharmacist has the moral responsibility for his activity towards patients, colleagues and society.

The pharmacist exercises his profession with respect for life and for the human person.

The pharmacist's moral duty is to ensure the accessibility and high quality of pharmaceutical assistance, the rational use of medicines, other pharmaceutical and parapharmaceutical products.

The pharmacist as a member of the community must contribute to informing and educating the public on health, social and ecological issues, combating drug addiction, sexually transmitted diseases, doping.

In any case, the pharmacist will behave in a manner appropriate to the dignity of the profession. Upon graduation from the faculty the pharmacists have the legal obligation to take the Professional Oath.

It is the duty of the pharmacist to propose to the attention of the society and the media bodies both the shortcomings and the achievements in the pharmaceutical activity.

(2) The professional responsibility and independence of the pharmacist

The pharmacist has the obligation to maintain the prestige of the profession and the prioritization of his knowledge in the field of medicine and pharmaceutical activity.

In exercising his functions, the pharmacist must maintain his moral, economic and professional freedom and independence.

In any place of work and whatever function he exercises, the pharmacist has the obligation to carry out personally the tasks incumbent upon him in granting the pharmaceutical assistance. It is forbidden to entrust one's obligations to other persons, except for legal substitutes.

The pharmacist has no right to apply his knowledge for anti-human purposes. The sole purpose of the pharmacist's activity must be the good of the patient or to the detriment of his own economic advantages.

Pharmacists have the obligation to continuously enrich their professional training through postgraduate recycling courses and through documentation from specialized publications on new discoveries in pharmaceutical theory and practice.

The pharmacist must promote good working relationships with the Pharmacists 'Association and as a member of it, pay the fee approved by the Pharmacists' Congress on time.

(3) Respecting the principles of pharmaceutical ethics and deontology

In his activity, including in the field of marketing and advertising of pharmaceutical products, the pharmacist must adhere to the rules of ethics and the ethical norms of drug promotion in the pharmaceutical market.

The basic principles in the professional activity must be to ensure the harmlessness, effectiveness, good quality and accessibility of the medicines in the treatment process and to respect the deontological norms between the partners in the pharmaceutical market.

Article 3. **Relationships between pharmacist and patient**

The pharmacist must respect the honor and dignity of the patient, having the obligation to assist all patients without discredit, in the order of their requests, except for emergency medical prescriptions.

At the time of release of pharmaceutical products, the pharmacist must inform the patients about the action of the drug (dose, route of administration, drug form, duration of storage, etc.).

If the patient's request cannot be fulfilled, the pharmacist should guide him to the nearest pharmacy in order to provide him with the medicines he needs.

To ensure that professional information is kept secret, pharmacists will not publicly discuss patients' diseases and their treatment.

The issuance of medicines without a prescription will be based on legal normative acts.

Pharmacists, within the limits of its competence, must provide emergency assistance to patients, in case of need.

Article 4. **Relationships between pharmacist and doctor**

The profession of pharmacist is incompatible with the profession of physician, and conversely, the profession of physician is incompatible with the profession of pharmacist. Thus, the pharmacist is not entitled to give medical advice, and the doctor is not entitled to provide pharmaceutical assistance.

Relationships between pharmacist and physician should be based on collaboration in the interests of patients.

The pharmacist should refrain from any act, which would harm the dignity of the physician, and the doctor should not undermine the pharmacist's authority.

The pharmacist will respond to doctors' requests regarding pharmaceuticals and will provide the necessary information regarding the medicines existing in the unit.

The collaboration of the pharmacist and the doctor is to be oriented towards the selection of efficient drugs, optimal pharmaceutical forms, rational treatment schemes, etc.

The high professionalism of the pharmacist is an essential criterion in establishing the collegial relations between the

pharmacist and the doctor.

Article 5. **Relationships between the pharmacist and his colleagues**

The pharmacist should behave with colleagues in such a way that they would like to behave with him.

Collective relationships are to be built on the basis of mutual esteem, goodwill, honesty and responsibility towards the collective purpose.

Pharmacists need to collaborate and help one another in fulfilling their professional duties, to show loyalty and solidarity towards one another.

It is necessary to keep in mind that the position does not give the manager of the pharmaceutical unit the moral right to lead, but only a higher level of professional competence.

The criticism against the colleague, being even expressed in a correct and argued form, is not allowed in the presence of patients. Attempts to gain authority by discrediting a colleague are inadmissible. At the same time, the pharmacist is obliged to condemn the incompetent actions of his colleagues or of the non-professionals that harm the patient's health.

Article 6. **Final provisions**

The requirements of this Code of Ethics are mandatory for all pharmacists in the Republic of Moldova. Responsibility for violating the provisions of the Code of Ethics is determined in the Statute of the Association of Pharmacists of the Republic of Moldova.

The right to review the Code of Ethics or to interpret certain theses from it belongs to the Pharmacists Association of the Republic of Moldova.

When registering as a member of the Pharmacists' Association, the pharmacist must become aware of the contents of this Code and undertake to fully respect it.

he concrete types of activity (tab. 1.1.) Included in the definition of pharmaceutical activity can be divided into two groups:

I – those that can be performed exclusively by specialists pharmacists and / or laboratory technicians;

II – which can be exercised by other specialists.

Table 1.1.

Classification of the concrete types of the pharmaceutical activity

Nr.	Group	Nr.	The concrete type of pharmaceutical activity
I.	Activities exercised exclusively by pharmacists and / or laboratory technicians	1.	Preparation of pharmaceutical forms in pharmacies.
		2.	Storage of medicines.
		3.	Supply and delivery of drugs to to the population, pharmaceutical and medical enterprises.
		4.	Management of pharmaceutical units and their subdivisions.
II.	Activities performed by pharmacists, doctors, chemists, biologists and other specialists.	1.	Research focused on drug creation.
		2.	Analysis and standardization of medicines.
		3.	Registration of medicines.
		4.	Production of medicines.
		5.	Quality control.
		6.	Medication information.
III.	Activities not included in the definition of "pharmaceutical activity"	1.	Promoting a healthy lifestyle.
		2.	Pharmaceutical care.
		3.	Import of medicines.
		4.	Promoting drugs on the market.
		5.	Pharmaceutical market study.
		6.	Representation activity of pharmaceutical companies.
		7.	Harmless destruction of medicines.
		8.	Coordination of the pharmaceutical system.
		9.	Pharmacy training activity.
		10.	Other specific types of pharmaceutical activity.

In addition, there are a number of specific types of pharmaceutical activity, which for various reasons are not included in the definition of this notion.

The pharmaceutical activity is performed by specialists with higher pharmaceutical studies (pharmacists) or middle (laboratory technicians) and the qualification corresponding to the requirements

established by the Ministry of Health.

It is established that pharmaceutical warehouses, pharmacies and their subsidiaries are run by pharmacists only. As an exception, pharmacies and subsidiaries of pharmacies located in rural localities can be run by laboratory technicians who have the qualification corresponding to the requirements established by the Ministry of Health.

In the public medical-sanitary institutions in rural areas where there is no pharmaceutical assistance, the pharmaceutical activity carried out within the category II subsidiaries of pharmacies, as an exception, can be exercised by medical workers who have practical knowledge in the pharmaceutical field in accordance with the requirements established by the Ministry of Health.

Foreign citizens and stateless persons who have pharmaceutical studies can exercise the pharmaceutical activity, after the equivalence and recognition of the study documents in the manner established by the law, under the same conditions as the citizens of the Republic of Moldova.

According to the provisions of law 1456/1993, a pharmacist (laboratory technicians) can only run a pharmaceutical company. The requirements established by the Ministry of Health regarding the level of qualification of the specialists performing pharmaceutical activity are presented in the tab. 1.2.

Table 1.2.

Mandatory qualification requirements for pharmacist specialists and pharmacist-workers, necessary for the pharmaceutical activity in the Republic of Moldova

Nr.		The name of the positions filled and the functions performed within the pharmaceutical company	Mandatory qualification requirements for filling positions
1.	a.	Pharmacist-Head	a Qualification category b Improving knowledge at least once every five years.
	b.	Pharmacist manager	
	c.	Head of branch of cat. I of community pharmacies	
	d.	Head of subsidiary of other types of pharmaceutical companies	
2.	a.	Deputy-Head Pharmacist	1. Qualification category 2. Improving knowledge at least once every five years.
	b.	Head of department	
	c.	Pharmacist Inspector	
3.	a.	Pharmacist expert	1. Improvement of knowledge at least every five years, except for young specialists in the first five years of activity.
	b.	pharmacist	
	c.	Pharmacist-technologist	
	d.	Pharmacist-analitician	
	e.	Labor-pharmacist	
Note: In pharmaceutical companies, located in rural localities, the positions and functions indicated in points 1 - a, b, c and 2 - a, b can be filled by pharmacist specialists or Labor-pharmacist, in the first five years after graduating the Faculty of Pharmacy or the College of Pharmacy. Medicine and Pharmacy, in the absence of the qualification categor.			

The exercise of the professions of pharmacist and laboratory-pharmacist is supervised by the Ministry of Health. According to the regulations in force, pharmacists and laboratory-pharmacist have the right and are obliged to continuously improve their professional knowledge

It is within the competence of the health protection bodies to organize the recycling of medical and pharmaceutical workers every 5 years in training institutions or faculties, in other institutions in the Republic and abroad.

According to the legal regulations, vocational training in the specialty "Pharmacy" is allowed exclusively in state educational institutions. Based on this legal norm, the Ministry of Health allows the pharmaceutical activity to be carried out only by the graduates of the pharmaceutical education institutions subordinated to the Ministry of Health.

Pharmaceutical activity for holders of state pharmaceutical education diplomas from other countries, is allowed based on the certification of knowledge by the Republican Commission for Professional Certification.

Practical application 1.1

1. *List the legislative and normative acts that regulate the order of employment and resignation of the specialists, the drafting of the individual employment contract and the material responsibility.*

The law on pharmaceutical activity regulates the following types of pharmaceutical enterprises:

- ✓ industrial pharmaceutical enterprises;
- ✓ pharmaceutical microproduction enterprises (laboratories);
- ✓ laboratories for quality control of medicines;
- ✓ pharmaceutical warehouses;
- ✓ pharmacies;
- ✓ pharmaceutical research institutions;
- ✓ scientific-practical pharmaceutical institutions.

Pharmaceutical enterprises may set up subsidiaries in accordance with the legislation in force. The right to organize subsidiaries is indicated in the founding documents of the pharmaceutical company. Pharmaceutical companies can be state and private. The state-owned enterprises also rank those of the administrative-territorial subdivisions (municipal, district, city)..

According to Healthcare Law, individuals and businesses may exercise pharmaceutical activity independently or dependent only on a license basis. The license to practice the pharmaceutical activity is an official act attesting the right of the holder to carry out this activity, for a certain period, with compulsory compliance with the licensing conditions and the requirements established by the Ministry of Health.

Community pharmacy is a pharmaceutical company belonging to the health care system intended and freely accessible to the general public, regardless of place of life, who benefit from pharmaceutical assistance in accordance with the legal regulations, including in medical emergencies, the basic task of which is the pharmaceutical activity multilateral to provide the population with timely and high quality assistance with medicines, parapharmaceuticals and other medical products and to provide other pharmaceutical services oriented to the benefit of the population.

As a enterprise the pharmacy is founded and liquidated in accordance with the legislation in force and the requirements established by the normative acts issued by the Ministry of Health or other state authorities empowered with such functions. It can operate on the basis of both types of property (private and state) and in any organizational-legal form provided by law.

In its activity the pharmacy is guided by the Law of health protection, the Law on pharmaceutical activity, the Law on medicines, the Law on entrepreneurship and enterprises, other laws of the Republic of Moldova, the Decisions of the Parliament and the Government, the normative acts issued by the Ministry of Health, other ministries, departments and bodies of local public administration.

The community pharmacy, as part of the health system, will operate according to the program established by the pharmacist-head, coordinated with the local public administration bodies. During the days of rest and holidays, the public pharmacies will be closed, except for the guard, according to the program established by the local public administration bodies.

The pharmacy has a firm, round stamp and header stamp. The company contains the full name of the pharmacy and its operating program.

Practical application 1.2.

1. *Get acquainted with all the documents based on which the pharmaceutical* enterprise *operates, with reference to the legislative and normative acts in force.*
2. *Draw up the layout of the pharmacy rooms.*
3. *Draw up the scheme of the collaboration relations of the pharmacy with the medical units.*
4. *Make the list of furniture and equipment specifying their destination and referring to the normative acts in force.*

The organizational structure of pharmacies is established depending on the workload, the functions it performs and its location in the territory.

As a rule, the following sections (subdivisions) can be organized in pharmacies:

- ✓ section of material stocks;
- ✓ production section;
- ✓ section for the production of industrial drug forms;
- ✓ section for the production of non-prescription drugs and parapharmaceuticals;
- ✓ service station with medical optics;
- ✓ branches of the pharmacy.

The number of sections, the way of combining different functions that the pharmacy performs are established depending on the concrete conditions of its activity.

Usually, in pharmacies with a small volume of work, no subdivisions are organized (except subsidiaries).

Depending on the character of the activity carried out, the community pharmacy may be of general profile (of industrial and / or production forms) or specialized in certain directions or genres of concrete activity. Separate rules and additional requirements may be set for specialized pharmacies (for children, herbs, etc.).

Practical application 1.3.

1. *Present the list of suppliers of pharmaceutical and parapharmaceutical products licensed in accordance with the legislation in force with which the pharmacy collaborates.*
2. *List the legislative and normative acts that regulate the organization of the keeping of pharmaceutical and parapharmaceutical products in the pharmacy.*
3. *Observe and note the rhythm of pharmacy space cleaning and ventilation operations.*

One of the functions of the pharmacy is the preparation and delivery of medicines according to the medical prescriptions (extemporaneous forms) or in the form of elaborations. To perform this function, pharmacies must have special rooms for this activity and permission to perform this function. Usually in such pharmacies a production unit is organized. The basic task of this section is the assistance of the population and of the medical-sanitary institutions or of another profile with medicines prepared in the pharmacy. n pharmacies with a high volume of work this section can be organized as a separate section, in other cases it can be combined with the material stocks section or another section.

The main function of the production section is to prepare the medicines according to the master prescriptions. In addition, in this section, purified water is prepared, concentrates, semi-products, medicines are produced in stock; from the section are delivered medicines to the population and to the medical-sanitary institutions; the section exercises the functions of control, information, granting of the premedical aid etc. of the medicines according to the master prescriptions.

In order to fulfill these functions, the department must have a series of rooms and equipment to ensure the technological process of drug preparation and quality control of the drug forms prepared, as well as to ensure an adequate level of the productivity of the work of the pharmaceutical personnel.

The production section is headed by the head of the section, who is responsible for the compliance with the sanitary and pharmaceutical regime in all the rooms of the section, for all the organizational work to ensure the preparation and delivery of quality medicines corresponding to the quality standardization documentation, for the correct receipt of the receipt. , by ensuring the integrity and the truthful and timely preparation of management reports on the circulation of material values. The nomenclature of the personnel of the production section includes: head of section, pharmacists, pharmacists-technologists, pharmacist-analyst, laborant-pharmacists, dividers, nurses, etc.

Practical application 1.4.

1. *Enter the agenda and charge 5 different prescriptions according to the pharmaceutical form.*
2. *Make for personal map all types of documents, which are kept in the work sectors in the drug preparation section.*

Example:

The final price of the extemporaneous drug form can be expressed by the following formula:

$$P_{fm} = \sum P_i + P_a + \text{“TL”}$$

where: P_{fm} – the price of the drug form;
$\sum P_i$ – the sum of the prices of the ingredients - components of the drug form;
P_a – the price of the packaging;
“TL” – “taxa laborum”.

Example of charging an extemporaneous prescription:

0-01,8	Rp.:	codeine phosphate 0,006
0-00,36		calcium glycerophosphate 0,01
3-60		paracetamolum 0,2
0-06		Glucosum 0,2
Pack. 0-50		M. f. pulvis
4-18,16		D. t. d. Nr. 30
TL 4-18		S. One powder three times a day after meals 10 days.
1-96		
1-68		
1-40		
1-12		
6-16		
10-34		

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Chapter 2.

QUALITY OF PHARMACEUTICAL SUBSTANCES AND FORMS. KNOWLEDGE OF THE DRUG.

Authors: **Vladimir Valica, Tatiana Treapitina, Livia Uncu**

The RM law regarding the drugs, No. 1409 - XIII of December 17, 1997, at national level ensures the access of the population to qualitative, efficient and safe preparations, as well as the prevention of the uncontrolled use of drugs.

Medicines, made through pharmacies, must meet the quality requirements of the Pharmacopoeia (European Pharmacopoeia) or the corresponding DAN.

During the State practice the student will fix his theoretical knowledge and practical skills, acquired during the study process in the compartments of this guide.

During the practice, the student must get familiarized with the principles of state control of the quality of medicines in the pharmaceutical units in the Republic of Moldova, in order to explore the range of medicines, to learn to evaluate the quality of medicines and to complete the relevant documentation.

This should ensure the execution of all types of quality control of medicines, considering the next rules:

- ✓ Laws and regulations regarding the standardization and quality control of drugs, their storage, compliance with health requirements and accident prevention, administrative and criminal liability for violations;
- ✓ system of control and quality assurance of drugs in the Republic of Moldova;
- ✓ pharmacopoeial drug analysis (physical, physico-chemical and chemical methods);
- ✓ analysis of magistral and industrial pharmaceutical forms in accordance with DAN requirements.

Quality monitorization of medicines is not only limited to testing according to DAN, but also to ensuring quality during drug storage.

The medicines are stored in specially equipped rooms, provided to ensure the quality of the medicines.

In the storage rooms the drug substances are distributed separately, in relation to:

- ✓ toxicological aspect:
  - ♦ group A - narcotic and psychotropic ("Poison- Venena ");
  - ♦ group B - energetically active substances ("Heroic" or "Separanda");
  - ♦ anodyne - substances from the general list;
- ✓ *administration mode (internal, external)*
- ✓ physico-chemical properties, taking considering the factors that exert a certain influence on the quality;
- ✓ the validity terms (for drug preparations with reduced validity terms);
- ✓ pharmacological and pharmacotherapeutical action;
- ✓ state of aggregation (liquids separated from powders, gases, etc.), for "en gros" drug substances;
- ✓ the character of different medicinal forms.

In the composition of the drugs are contained substances with different chemical structure, and with different properties, which require proper storage conditions: protection from the action of the sun rays, humidity, excessive heat, etc.

The drugs quality affects not only the storage conditions, but also the correct choice of the primary packaging, as well as the reasonable term of validity of the medicines.

Depending on the structure and the physical-chemical properties of the active principles, the term of validity may vary, being conditioned by the presence or absence of the degradation processes under the influence of external factors or internal factors, as well as the speed of these processes.

Spending the practical internship, the student must know:

- ✓ The laws of the Republic of Moldova, the Orders and Instructions of the Ministry of Health and of the Normative Documentation of Production, control and storage of medicines in pharmacies (order № 06,

10, 28 MS Republic).

- ✓ The state system of drug quality control.
- ✓ Common methods of analysis according to the current edition of the Pharmacopoeia (Ph.Eur.)
- ✓ Achievements of researches on the development of new drug substances and on improving the existing methods for evaluating the quality of medicines.
- ✓ Prescription rules for all types of medicines, including: toxic, narcotic and highly active drugs, maximum doses of substance for one or 24 hour intake.
- ✓ The sanitary, aseptic and antiepidemic requirements, the pharmaceutical legislation in force.

After completing the production practice, the student must be able to:

- ✓ to use reference bibliography, normative acts, orders and instructions for quality control of medicines in pharmacies
- ✓ to comply with the rules of the health regime;
- ✓ to carry out the quality control of the drug substance and to identify the errors, to make proposals for their prevention and elimination;
- ✓ to identify the physical, chemical and pharmacological incompatibility in the production and delivery of drugs;
- ✓ to carry out practically all types of quality control for master pharmaceutical forms;
- ✓ to carry out the analysis of medicinal plants according to the "external aspect" parameter;
- ✓ to monitorize the compliance of the storage conditions and the validity of the medicines.

During the practice the student will complete the practical applications, stipulated in the practice guide, filling in the guide immediately the tables according to the given examples.

Practical application 2.1.

During the practice in the IPUSMF University Pharmacy «Nicolae Testemitanu», the student must complete and describe the complete analysis **of five** magistral pharmaceutical forms, containing two or more components. The results must be recorded in the following table:

Composition of magistral pharmaceutical form	Description of the exterior appearance	Methods of identification. The equations of the chemical reaction	Dosage methods. The equations of the chemical reaction.Calculation formulas (calculation of the quantitative content of active principles and deviations).	Quality assessment
Alcohol solution of iodine 5% - 20,0 Comoisition Iodine 5,0 g Potassium iodide 2,0 g Water and alcohol 95% in equal parts up to 100.0 ml	Transparent liquid, brown color	***Iodine.*** One drop of drug form is diluted with 10 ml of water and 1 ml of starch solution is added; a blue color appears.	***Iodine.*** 1 ml of the drug form is transferred to a 100 ml conical flask with a running stopper and titrated with 0.1 mol / l sodium thiosulphate solution until discolored. 1 ml of sodium thiosulphate 0.1 mol / l corresponds to 0.01269 g iodine, which in the preparation should be 4.9-5.2%. $I_2 + 2Na_2S_2O_3 \rightarrow 2\,NaI + Na_2S_4O_6$ $\omega = \frac{V_B^2 \cdot T_{B/A} \cdot K}{a} \cdot 100$ Calculation of the deviation 5,0 -------- 100% 4,95 -------- X ; X = 99% Deviation 99 -100 = -1% Permissible deviation: ±5,0% **Potassium iodide.** 25 ml of water, 2 ml of diluted acetic acid, 5 drops of sodium eosinate are added to the titrated solution and titrated with 0.1 mol / l silver nitrate until the liquid becomes pink.	The pharmaceutical form is prepared satisfactorily.

			After the difference of the volumes of 0.1 mol / l silver nitrate (V1) and 0.1 mol / l sodium thiosulphate solution (V2), the content (%) of potassium iodide is calculated: 1 ml of silver nitrate 0.1 mol / l corresponds to 0.01660 g of potassium iodide, which in the preparation must be 1.9-2.1%. **KI + 2NaI + 3AgNO$_3$ → 3AgI↓ + KNO3 + 2NaNO$_3$** $\omega = \frac{(V_B^1 \cdot K^1 - V_B^2 \cdot K) \cdot T_{B/A}}{a} \cdot 100$ Călcularea abaterei Calculation of the deviation 2,0 -------- 100% 2,08 -------- X ; X = 104% Deviation 104 – 100 = +4% Permissible deviation ±5,0%	

Practical application 2.2.

Comparative analysis of 5 industrial pharmaceutical forms existing in the community pharmacy where you spend the practical internship, according to the parameter "Description" according to the requirements of DAN, European Pharmacopoeia or Romanian Pharmacopoeia. The results are recorded in the following table, following the example:

The name of the drug and its composition	Therapeutic indications	DAN requirements	Results
500 mg / 5 ml ascorbic acid injection solution	Treatment of avitaminosis C, infectious diseases, poisoning, liver, lung, uterine diseases.	Transparent and colorless solution. An eventual staining should not be more intense than staining a solution prepared from 0.10 ml cobalt-E.c., 0.20 ml copper-E.c., 0.75 ml iron-E.c. and water to 10 ml.	Transparent and colorless solution. The color of the solution may vary depending on the violation of storage conditions. Ascorbic acid oxidizes under the action of light. If the color is more intense in relation to the provisions of the DAN, it is forbidden to release the drug from the pharmacy.

Practical use 2.3.

Explanation of the choice of the primary packaging, the storage conditions and the term of validity for 5 industrial drugs existing in the community pharmacy where you spend the practical internship, depending on the physical and chemical properties of the components of the pharmaceutical form. The results are recorded in the following table, following the example given:

The name of the drug, the DCI of the active ingredients, the manufacturer	Therapeutic indications	Results		Explanations
Metamizole sodium tablets 500 mg No. 10, Analgine. Pharmaco SA	Nerves, myositis, radiculitis, headache, rheumatoid arthritis, fever	Primary packaging →	In blisters	Protecting the tablets from the action of external factors (moisture, microorganisms) throughout the period of use, convenience of use.
		Storage conditions →	Separanda. Internal. Protected from light.	It is kept according to list B, because it is a very active preparation. It must be protected from light, because pyrazole derivatives are easily oxidizable. As a result, the tablets may turn yellow.
		Terms of validity →	4years	When the primary packaging and storage conditions are properly chosen, the drug substance is stable.

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Chapter 3.

DRUGS PREPARATION IN THE PHARMACY.

Authors: **Diana Guranda, Cristina Ciobanu, Rodica Solonari**

The *pharmacy* is a curative-prophylactic institution that provides qualitative medicinal help to the population in a timely and accessible way. The production department's main problems are the preparation and dispensing of pharmaceutical forms according to medical prescriptions and order-delivery bills from curative-prophylactic institutions. The production function is reduced to the preparation, quality control and delivery of pharmaceutical forms.

Objectives:

The student must participate in activities and to get acquainted with:

- ✓ internal organization rules (working schedule, conditions, discipline);
- ✓ security technique;
- ✓ the pharmacy personnel preparing extemporaneous pharmaceutical forms;
- ✓ personnel's obligations;
- ✓ preparation areas, preparation equipment, how to organize the activities for the preparation process of a pharmaceutical form and the cleaning specifics for the areas in compliance with the sanitary regime;
- ✓ preparing auxiliary tools and equipment;
- ✓ raw materials and their role in the preparation technology of a pharmaceutical form;
- ✓ optimal technologies and their conditioning;
- ✓ how to label a product based on its purpose;
- ✓ storage conditions based on the preparation's physical-chemical characteristics in order to ensure its stability;
- ✓ registers for records and registration of quality control.

Drugs prepared in the pharmacy

The preparation of drugs in the pharmacy aims to: condition some medicinal substances as such (xeroform, boric acid, glucose); prepare some excipients for drugs and that are stored in the pharmacy (purified water, simple syrup etc.); prepare officinal forms for preparations (furacilin solution, rivanol solution etc.).

The specific preparation activity is conducted in order to obtain magistral drugs or some elaborated formulations:

Magistral drugs: are prepared according to medical prescriptions for patients. Most often, there are prepared pharmaceutical forms that are not dispensed by the pharmaceutical industry. The preparations are prepared individually for the patient as well as for a curative-prophylactic institution.

Elaborated formulations: are prepared based on established prescriptions and that are often encountered in extemporaneous drug preparation.

Drugs preparation:

In order to prepare a qualitative and stable preparation in a timely manner, the pharmacist must follow the norms of the instruction regarding the sanitary regime in the pharmacy which includes the following requirements:

- space and equipment;
- cleanness in the area;
- personal hygiene;
- obtaining and storing purified water;
- preparation of sterile and non-sterile forms;
- treatment and washing of rubber caps;
- washing and drying of pharmaceutical dishware.

The preparation stages of extemporaneous forms in the pharmacy:

While analyzing the medical prescription, the pharmacist pays attention to:

- ✓ The requirements of Order of MH No. 960 as of 10.01.2012 "On how to prescribe and dispense drugs"
- ✓ The compatibility of active substances and auxiliary substances
- ✓ Verification of single and nictemeral doses for toxic, stupefying, and highly active substances according to age (in case of non-compliance to dispense half of the single maximum dose from the RP X).
- ✓ Choosing excipients and auxiliary substances in order to ensure the compatibility with the active substances and based on the disease's specifics (diabetes, allergy, etc.).
- ✓ Identifying difficult prescription that require to choose optimal variants for their elimination (changing some active and auxiliary substances with others having the same therapeutic action, introducing an optimal preparation variant, etc.).

Establishing the quantity of elaborated preparation

The nomenclature and quantity of the stock of products prepared in the pharmacy depends on the quantity of prescriptions that are encountered often in extemporaneous drug preparation.

Preparing the preparation area

The drugs preparation activity in the pharmacy is conducted in the drug preparation area in compliance with the "Sanitary regulation regarding the equipping and use of pharmacies and pharmacy depots" (approved by Government Decision No. 504 as of 07.12.2012). The drug preparation area is isolated from other areas of the pharmacy. The equipment and furniture are installed so as not to leave inaccessible spaces for cleaning and not to block light sources. The walls and ceiling of production areas are finished with chemo resistant materials that allow wet cleaning and use of disinfectants. The surface of the pharmaceutical equipment must be smooth, made from materials resistant to the action of drugs, and in some cases also to chemical reagents.

Preparing the working conditions

The technological process in the pharmacy must include appropriate equipment and precise measuring objects that are regularly subject to State control. While choosing raw materials, auxiliary substances, etc., the pharmacist takes into account their action on the quality of the finished product. Particular attention is paid to obtaining purified water.

Before the main preparation:

- ✓ The dishware and tools are chosen based on: quantity of preparation; physical-chemical characteristics of active and auxiliary substances; compatibility of substances with packing material; components' photosensitivity.
- ✓ Based on Order of MH RM No. 960 as of as of 10.01.2012 "On how to prescribe and dispense drugs", all pharmaceutical forms are labeled with standard labels depending on the area of use (internal, external, for injections, ophthalmic) having different colors. All the labels must include: symbol of medicine, pharmacy No., prescription No., patient's first and last names, how to use, preparation date, signature of the pharmacist who prepared the form, cost, additional information, "Keep out of reach of children".

Pharmacist's preparation for work

The pharmacist's equipment must ensure the obtainment of a final product of quality (Order of MH RM No. 334 as of 07.19.1995 "On the approval of the Instruction regarding the sanitary regime in pharmaceutical companies and institutions".)

The actual technological process, drug's packaging and quality control

The regulation of the technological process is one of the factors at the bases of obtaining a quality product. The general incipient stage of any technological process is preparatory work: conformity of raw material with quality norms. After the preparatory stage, there takes place the succession of technological process stages in accordance with the medicinal form's specifics. During the working process, the general rules must be taken into account: mixing, dissolving based on the medicinal substances' physical-chemical properties, the provisions of the pharmacopoeia and the conditions of the pharmacy. The final stages of the technological process are standardized for all medicinal forms: packaging and preparation for dispensing. All

preparations are packaged depending on the state of aggregation, route of administration, etc.

During the working process the pharmacist is obliged to observe: all stages of the preparation technology flow must be in compliance with the NAD norms. Each stage must ensure the quality, safety and effectiveness of the final product. The ultimate goal is to obtain a preservable, qualitative and stable product.

In order to avoid confusion, the pharmacist must pay special attention when choosing the substance's label. Special attention is paid when working with active substances (toxic, stupefying, highly active) with their mandatory written registration.

The final product's analysis includes the following types of verification:
- ✓ organoleptic (color, odor, aspect);
- ✓ written;
- ✓ physical;
- ✓ chemical (according to NAD requirements).

Before the medicinal form's preparation, calculations are made on the back of the written verification document (WVD). When using semi-finished products and concentrates, their concentration and quantity must be written. When preparing powders, suppositories, there must be written the mass of individual doses and their quantity. The quantity of the suppository mass, the quantity of stabilizing substances that are to be added in ophthalmic drops and solutions for injections are written in the WVD and on the back of the prescription. The passport includes the coefficient of volume expansion of aqueous solutions when dissolving medicinal substances, the soaking coefficient of the medicinal vegetal product. After the preparation process, the WVD is filled in by memory, immediately writing: date; prescription No.; succession, quantity of medicinal substances, No. of doses, signature of the pharmacist who prepared, controlled and dispensed the pharmaceutical form. For the forms containing toxic, stupefying substances, at the top of the WVD, the letter "A" is written and for the forms for children the letter "C" is written.

Pharmaceutical forms labeling

On the preparation's label it is mandatory to write: pharmacy No., extemporaneous prescription No., preparation date, expiration date, information about administration, use and storage of the pharmaceutical form, signature of the pharmacist who prepared the form. For extemporaneous drugs, the label is chosen depending on the route of administration: internal use or external use.

Extemporaneous forms' storage conditions and terms

The terms and conditions for storing extemporaneous forms must ensure the physical, chemical and microbiological stability based on the properties of the medicinal and auxiliary substances and the pharmaceutical form. According to the NAD (Order No.10 as of 01.06.2006 "On the supervision of the quality of medicinal forms prepared in pharmacies" and the annex "Terms of validity and sterilization conditions of the pharmaceutical forms prepared in pharmacies" which includes the storage terms and conditions for internal use solutions in hermetically sealed flasks with rubber or polished caps, for newborns, eye drops and ophthalmic solutions in flasks and bottles hermetically sealed with hermetic rubber caps, other pharmaceutical forms - mixtures and solutions for internal use, concentrates, etc. The terms of validity of medicinal forms prepared in the pharmacy that are not included in the annex are: for ophthalmic drops - 2 days; for infusions, decoctions, mucilage - 2 days; for emulsions, suspensions - 3 days; for other extemporaneous pharmaceutical forms - 10 days.

Registration of drugs prepared in the pharmacy

The record of extemporaneous pharmaceutical forms is kept in the registers *for extemporaneous forms* in which it is mandatory to write: prescription No., date, composition; *for pharmaceutical preparations* it is written: date, series, composition, quantity of components used for preparation and quantity of preparations, analysis No., pharmacists' last names.

Practical application 3.1.

1. *Familiarize yourself with the pharmacy's areas, their furniture and necessary equipment. Study the provisions of*

the Government Decision No. 504 as of 07.12.2012 on the approval of Sanitary regulation regarding the equipping and use of pharmacies and pharmacy depots and write in your notebooks the main sections. Draw in the notebook the components and positioning of the pharmacy areas (drug preparation area) and enumerate the area's equipment.

2. Study the equipment for obtaining purified water, quality control and its keeping. Write in the notebook.

3. Get acquainted with the Instructions regarding the pharmacy job security technique. Write in the notebook the main sections of the Instructions, as well as the Registers on job security of the pharmacy's personnel.

4. Get acquainted with the Instructions regarding the sanitary system and personal hygiene in the pharmacy. In the notebook describe the main sections of Order of MH RM No. 334 as of 07.19.1995 "On the approval of the Instruction regarding the sanitary regime in pharmaceutical companies and institutions". Describe the pharmacy cleaning specifics.

5. Get acquainted with Order of MH RM No. 960 as of 10.01.2012 "On how to prescribe and dispense drugs". In the notebook describe the main sections.

6. Participate in the preparation activities in the pharmacy and write: preparations that are conditioned and dispensed as such from the pharmacy, preparations that are prepared based on medical prescription, pharmaceutical preparations, products that are prepared and kept in the pharmacy in order to be used at other drugs' preparation.

7. Get acquainted with the prescriptions received by the pharmacy. Get acquainted with all the information contained in these forms. Describe the pharmacist's working procedure in case of finding errors in a prescription. Give a few examples.

8. Get acquainted with the preparation registers (reception register, preparations register) and describe in the notebook the method of registration for 2-3 pharmaceutical forms in the pharmacy.

9. Study the pharmacopoeia regarding the general provisions on pharmaceutical forms preparation, their quality characteristic, and storage conditions (Order of MH RM No. 113 as of 02.17.2011 "On the approval of Pharmacopoeias of reference in the Republic of Moldova").

Model of answer for the preparation of a pharmaceutical form:

1. Prescription's composition. Compatibility. Verification of doses.

Rp.: Sol. Citrali spirituosae 1% - 2 ml
Coffeini -natrii benzoatis 0.2
Magnesii sulfatis 3.0
Natrii bromidi 2.0
Tincturae Valerianae 2 ml
Sol. Glucosi 10%- 200 ml
M.D.S. Internally. One table spoon, 3 times a day, after meals.

The ingredients are compatible
Verification of doses: ***Caffeine and sodium benzoate (list B):***
Total volume of the mixture 204 ml. The volume of a table spoon is 15 ml.
Number of administrations: 204: 15 = 14.
the dose prescribed for a single time: 0.2: 14 = 0.01 gr
the dose prescribed for 24 hours: 0.01 x 3 = 0.03 gr
Verification with maximum doses of Romanian Pharmacopoeia ed. X:
maximum dose for a single time: 0.5gr
maximum dose for 24 hours: 2.0gr

The doses are not exceeded.

2. Physical-chemical proprieties of the medicinal substances.
Storage. Indications.

Citral alcohol solution of 1%: Transparent liquid, with odor and taste specific to citrus fruits (lemon). It is prepared on alcohol of 95% from citrus ethereal volatile oil. Pharmacological action - analgesic and anti-inflammatory. Keep in a cool place and away from light.

Caffeine and sodium benzoate: White powder, without odor, with bitter-sweet taste. Easily soluble in water, slightly soluble in alcohol, difficultly soluble in chloroform. Stored in tightly closed containers. Separandum (list B). Pharmacological action - excitant of the central nervous system.

Magnesium sulphate: White crystalline powder or colorless crystals, without odor, with a cooling, salty and bitter taste; efflorescence. Very easily soluble in water, practically insoluble in alcohol. Stored in tightly closed containers. Pharmacological action - laxative, purgative, anticonvulsant, used in the treatment of hypomagnesemia.

Sodium bromide: White crystalline powder, odorless, salty, hygroscopic. Easily soluble in water, soluble in alcohol. Stored in tightly closed containers. Pharmacological action - sedative.

Valerian tincture: Clear, red-brown liquid, with specific odor and taste and weak acid reaction. Alcohol content of at least 52.5%. Pharmacological action – sedative.

Glucose: Synonym: dextrose. White crystalline powder, odorless, with sweet taste, hygroscopic. Soluble in water, alcohol,

difficultly soluble in ether, very difficultly soluble in acetone. Pharmacological action - caloric intake in parenteral nutrition, sweetener.

3. Characteristics and preparation of the medicinal form. Dispensing.

Liquid medicinal form - opalescent mixture containing highly active substance - caffeine and sodium benzoate; anodyne substances: magnesium sulfate and glucose; photosensitive substance - sodium bromide; alcoholic extractive solution - valerian tincture and volatile and odorous solution - 1% citral alcohol solution.

Preparation technology:

In the pharmacy there are no concentrated solutions of medicinal substances, so we will prepare the mixture by dissolving the solid medicinal substances. The percentage content of the prescribed solid substances is 12.3%, so it is more than 3%, for the correct and precise calculation of the quantity of purified water, we will use the coefficient of volume expansion of the aqueous solution when dissolving medicinal substances.

184 ml of purified water is poured into a glass container where there are dissolved 0.2 g of caffeine and sodium benzoate (list B), 20.0g glucose, 3.0g magnesium sulfate, 2.0g bromide of sodium (based on solubility). The resulting solution is strained into the brown delivery flask where 2ml of valerian tincture is added. In another container 2ml of prepared mixture is put and mixed with 2ml of 1% citral alcohol solution (it is prepared on 96% alcohol), the obtained solution is added to the prepared mixture. The flask is labeled “For internal use” with the mention “Keep in a cool place", "Shake before use", " Keep out of the reach of children".

Calculations:

Total volume of the mixture: 200ml + 2ml+2ml=204ml

Volume of the purified water 204ml – (3.0g x 0.5ml/g + 2.0g x 0.26ml/g + 20.0g x 0.69ml/g+4 ml) = 184ml

Written verification document:

date Prescription No.

Aquae purificatae 184ml
Coffeini-natrii benzoatis 0.2
Glucozi 20.0
Natrii bromidi 2.0
Magnesii sulfatis 3.0
Tincturae Valerianae 2ml
Sol. Citrali spirituosae 1% - 2ml

Total volume = 204ml
Prepared by:
Verified by:
Dispensed by:

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Chapter 4.

THE DELIVERY OF THE MEDICINAL PRODUCTS AND THE ADVICE OF THE PATIENT.

Authors: **Mihail Brumarel, Stela Adauji, Liliana Dogotari, Corina Scutari, Elena Bodrug**

Delivery of prescription drugs

Before to the release of drugs, the pharmacist has the duty to analyze the medical prescription, as provided by the Order of the Republic of Moldova no.960 from 01.10.2012.

1. The pharmacist verifies the medical prescription from the point of view of the form:
   - ✓ appropriate prescription form, according to the legislation in force;
   - ✓ identification of the doctor who prescribed the drug.
2. The pharmacist identifies the patient (for whom are the medicines?)
3. The pharmacist analyzes the prescribed drug therapy:
4. The pharmacist determines the pharmacological classes of the the prescribed drugs: necessary attitude to determine the therapeutic objectives (the doctor's intention); identification of drugs with a narrow therapeutic area, which require increased attention.
5. The pharmacist checks if the patient has used the prescribed medicines: talk to the patient or his representative, the outpatient record.
6. The pharmacist obtains information about the patient, which may influence the response to drugs:
   - ✓ age, weight, sex;
   - ✓ pathophysiological state: pregnancy, lactation, renal impairment, liver failure, heart failure, allergic history;
   - ✓ alcohol consumption, smoking, diet (deficient diet, hypoglycemic diet, vegetarian diet with risk of protein deficiency, etc.);
   - ✓ psycho-social status; profession, economic situation, living conditions, mental state.
7. The pharmacist evaluates the contraindications of the prescribed drugs: depending on the physiopathological condition of the patient.
8. The pharmacist checks the dosages and the administration of the drugs:
   a. The dose: to be within the therapeutic limits
   b. Method of administration: the dose can be easily measured and administered (no teaspoons, no drops, no inhalations, etc.); to correspond to an existing pharmaceutical form
   c. Frequency of administration: - to take into account:

- *the pharmaceutical form of the drug;*
- *the pharmacokinetic properties of the drug substance;*
- *physico-chemical compatibility of the drug substances, in case of association of injectable mixtures.*

9. The pharmacist determines the product to be released, and if there are several products that contain the same active substance, in the same concentration (generic products): check whether the pharmaceutical form is of immediate or prolonged action, attention in case of narrow therapeutic drugs.
10. The pharmacist compares the cost differences between existing products containing the same active substance: the pharmacist decides with the patient on the product to be released; In case of compensated or free regime prescribed drugs, substitution is allowed according to the regulations in force.
11. The pharmacist evaluates the possibility of interactions with clinical consequences:
    - ✓ drug-drug interactions: drugs from the respective prescription;
    - ✓ with other prescription drugs;
    - ✓ with drugs from self-medication. drug-food interactions;
    - ✓ drug interactions - biological analyzes.
12. The pharmacist establishes the patient's attitude to prevent/reduce the adverse effects of the interactions.
13. The pharmacist determines the precautions for use and the adverse effects of the prescribed drugs:

for the purpose of monitoring the therapy and informing the patient.

14. The pharmacist establishes/indicates the hours of administration of the drugs: according to the doctor's recommendation, the chronopharmacology data, pharmacokinetics properties, adverse effects, galenic characteristics.

15. The pharmacist advises the patient in order to obtain the positive results of the treatment necessary information for the patient:

- ✓ action of drugs,
- ✓ dosage of drugs,
- ✓ administration mode,
- ✓ duration of treatment,
- ✓ any adverse effects,
- ✓ interactions
- ✓ precautions to be followed,
- ✓ biological, clinical and/or paraclinical parameters to be followed during treatment,
- ✓ how to store med drugs (to ensure physico-chemical and microbiological stability, to prevent accidents)
- ✓ other recommandations (lifestyle, sources of information).

16. The terms used must be simple, in order to be understood by the patient; - it is necessary to verify the understanding of the information by the patient, asking the patient, at the same time, to put questions if he has any doubts; if is necessary, the information will be repeated;

15. For a better understanding the information will be communicated also in writing or with the help of other methods (brochures, leaflets, etc.), not just in writing; the information will be given by showing the patient the box or vial of the drug referred to;

16. In case of devices that require specific handling (eg.: devices for inhalation) it is advisable for the pharmacist to perform a demonstration to ensure that the patient has understood the correct mode of use.

17. The pharmacist will draw up a schedule of drugs for once day (schedule of prescriptions), setting the times at which the patient should administer his medications (according to the doctor's recommendations, characteristics of the drug and daily schedule or patient preferences) and which he will transmit it to him.

18. The pharmacist encourages the patient to return to the pharmacy to evaluate the treatment results: the patient followed/did not comply with the recommended treatment (compliance); the patient considers the treatment to be efficient/inefficient; the patient informs the appearance of adverse effects.

Practical application 4.1.

Analyze in writing, according to the model below, 10 medical prescriptions in the pharmacy where you practice (the prescriptions hierarchy will be annexed)

Algorithm for analyzing the prescription

- ✓ *receiving the recipe and verifying the authenticity of the content:*
  - *the personal data of the patients: name, surname, age, etc .;*
  - *the validity of the prescription and the correctness of the prescription (according to the order of the RM no.960 from 01.10.2012)*;
- ✓ *pharmaceutical evaluation of the prescription:*
  - *if the prescribed medicines are allowed to outpatients;*
  - *if the recipe contains:*
    - ➢ *patient data;*
    - ➢ *name of the drug;*
    - ➢ *dose;*
    - ➢ *amount;*
    - ➢ *date of prescription;*
    - ➢ *signature and stamps required.*

- *if the recipe is valid;*
- *if all the required stamps are present (as appropriate);*
- *verify that:*
  - ➢ the prescribed drugs, according to the pharmaceutical form and the mode of administration, correspond to the patient's state;
  - ➢ the prescribed dose corresponds to the admissible limits and the personal parameters of the patient: age, weight, etc., especially in case of drugs for children and oncological patients;
  - ➢ the required quantity of drug is prescribed;
  - ➢ interaction with other drugs administered by the patient is possible;
  - ➢ there are contraindications for this drug;
  - ➢ there are adverse effects, about which the patient must be informed;
  - ➢ it is possible the non-compliance, incorrect or abusive use of the drug by the patient.

✓ *interventions and problem solving;*

- *If any of the above problems arise, contact the doctor who prescribed the prescription with the pharmacist and resolve the case;*
- *if will be changes in the prescribed treatment, to note them in the Register of interventions record;*
- *Once convinced of the validity and correctness of the prescription, go to the next steps of the drug delivery procedure;*

✓ *completion and control - before delivery, the pharmacist must check:*

- *the compliance of the drug with the prescription;*
- *the term of validity of the drug;*
- *the integrity and label of the package;*
- *the presence of the instruction for use in the language understood by the patient;*

✓ *drug delivery - the pharmacist must check if:*

- *the drugs are delivered to the appropriate person;*
- *the patient signed the prescription (in case of compensated ones);*
- *the patient received and understood the necessary information;*
- *the delivered drugs have dosing spoons or pipettes (if necessary);*
- *hygiene and safety rules are respected.*

✓ *monitoring of treatment:*

- *the pharmacist will participate, together with the doctor, in the evaluation of the treatment applied to a patient respecting confidentiality;*
- *If adverse effects are recorded during the treatment, the pharmacist will complete the Notice of adverse reactions of medicines and other pharmaceuticals and submit it to the* Medicines and Medical Devices Agency**.**

Practical application 4.2.

1. Describe 5 cases of pharmacist-patient communication in the process of OTC drug delivery and for each case fill in the following table:

Description of the patient's problem	Recommended drug and dosage regimen	Critical analysis of the solution applied	Recommendations regarding patient monitoring	Consultation of the patient by the pharmacist
The 37-year-old patient addresses to the pharmacy, requesting a medicine for sore throut, dry cough	Isla-Mint Herbal was recommended for patient. It has antitussive, antimicrobial, expectorant, immunostimulatory action, forms a protective film, which protects from external factors and irritants. 1-2 pills per day.	The patient assumes that the state is determined by the overload of the vocal cords, because he is a teacher and has been cold for a long time.	Avoid the influence of the harmful conditions - cold and wind, pause in the professional activity, in case the symptoms do not disappear, go to the doctor.	The pharmacist establishes the period of onset of symptoms, the taken measures, the establishment of anamnesis and accompanying diseases. Consult the doctor in order to establish the definitive diagnosis, to avoid chronicling the process.

Description of the patient's problem	Recommended drug and dosage regimen	Critical analysis of the solution applied	Recommendations regarding patient monitoring	Consultation of the patient by the pharmacist

2. Identify, in the pharmacy where you practice, the drugs used to treat the symptoms that are characteristic for

2.1. respiratory infections: sore throat, rhinitis;

2.2. respiratory infections: cough, cold, fever, conjunctivitis;

2.3. central nervous system disorders: headache, anxiety;

2.4. disorders of the locomotor system: osteoporosis, osteoarthrosis;

2.5. disorders of the locomotor system: arthralgia, myalgia;

2.6. dermatological disorders: mycosis, seborrhea;

2.7. dermatological conditions: herpes, acne;

2.8. polyhipovitaminosis, avitaminosis

2.9. gastrointestinal tract disorders: constipation, diarrhea;

2.10. gastrointestinal tract disorders: flatulence, hemorrhoids
according to the model below:

Name of Medicine (Trade name)	INN or active substances	Presentation form	Classification	Precautions / contraindications	Adverse effects	Consultations for the patient
Cefecon® D, supp. 100 mg N 5x2	Paracetamolum	Suppositories	Rx	Hypersensitivity to the preparation, severe hepatic and / or renal failure, glaucoma, urinary retention, blood diseases, pregnancy, lactation, under 3 months.	Anemia, agranulocytosis, thrombocytopenia, allergic reactions.	children 3 months-1 year 25-50 mg 2-4 times daily, 2-5 years 100-150 mg 2-4 times daily, 5-10 years up to 1000 mg / day, 10-15 years up to 1500 mg / day.

Compliance with the treatment (therapeutic adherence)

The role of informing and training the patient (counseling the patient) contributes to achieving optimal compliance and therapeutic success.

The directions of information and training of the patient refer to:

- ✓ *Purpose of treatment and effects of pharmacotherapy:*
  - what symptoms and disorders will disappear and when;
  - dosages and administration of medicines;
  - the route of administration, the correct way of administration;
  - the optimal time of administration in relation to meals and the circadian biorhythm;
  - the interval between administrations;
- ✓ *Precautions and contraindications related to:*
  - driving;
  - nutrition, alcohol, tobacco;
  - self-medication;
  - foreseeable side effects of medication;
  - manifestations, severity, duration;
  - immediate reporting of the occurrence of side effects.

Compliance (adherence) = behavior of the patient what plays a fundamental role in the success or failure of any treatment final. Compliance check (correctness of the patient's prescription) must be performed carefully. Compliance → is essential for effective and safe pharmacotherapy.

Non-compliance can lead to:

- treatment inefficiency
- manifesting the undesirable effects of the drugs

Improving patient adherence to treatment and optimizing compliance → applicable measures on patient behavior - a fundamental role in the success or final failure of any treatment; necessary condition (not enough) for therapeutic success.

Common causes of treatment failure

- ✓ *Prescription of improper galenic forms*
  - the elderly can lead to an underdose or overdose (e.g.: bad use of a pipette) or suppression of drug (e.g.: suppository).
  - in children can lead to serious accidents (tablets in children under 3 years)
- ✓ *The pharmacist must inform the patient about the operation of special devices for administration of certain drugs (aerosol dispensers, inhaler powder dispensers, ointment application systems, suppositories, etc.)*
  The proper handling of these devices is the guarantee of the optimal therapeutic efficacy, as well as the avoidance of the sometimes-serious adverse effects.
- ✓ *Loss of visual acuity and decreased dexterity in the elderly directly influence the behavior of the dosage.*
  More than 50% of the elderly do not follow the prescription correctly and about 25% are "involuntarily" mistaken
- ✓ *Inadequate organoleptic properties of medicines* may result in non-acceptance, especially in children
- ✓ *Mild side effects* (e.g.: dry mouth, constipation, cough, etc.) may cause the patient to stop the medication
- ✓ *Distribution of administrations during the day* may be inappropriate for a person who they will work and during illness; the "practical" solution adopted by the patient will be:
  - or that of two-dose cumulation (e.g.: noon and morning),
  - or that of changing the rhythm of the administrations (e.g.: suppressing one of them).
- ✓ The *route of administration.*
  - The rectal and local routes are usually poorly followed.
  - These routes of administration are often mistakenly considered by the patient to be "minor".
  - The pharmacist must explain the role of these routes of administration whose choice was in the therapeutic interest.
- ✓ *Psychological context and environment of the patient*
  - a serious pathology is often the subject of good compliance, especially if this disease is known to be curable;
  - for some patients no. of tablets and the administration regimen is a painful moment for their condition and these patients may try to avoid this reminder by discontinuing the medication;
  - on the contrary, benign diseases or isolated symptoms (e.g.: diarrhea, constipation, etc.) are the subject of approximations, that is, the therapeutic "attempts" of the patient;
  - some patients reduce or even discontinue treatment (on their own initiative), proving that they are less or not at all ill.
- ✓ *Memory loss*
  In the case of "memory loss" (which may also be of iatrogenic origin), the pharmacist will be careful to record in writing the tips and recommendations related to the prescription. By accompanying a prescription with written information, the pharmacist ensures that the patient will follow the treatment correctly.

- ✓ *Age, sex and level of education*
  - The older person who "has never been sick" will probably not get his treatment, even if he comes to the pharmacy for dispensing the prescription.
  - Whether the medicine is important (e.g.: cardiovascular) or less important, it can be considered as a "drug" by the patient and thus a source of harmful effects.
  - Women are more consistent in treatment than men.
- ✓ The *doctor may be the indirect cause of a non-compliance with the treatment.*
  - a complicated, improperly explained (or incorrectly written) prescription or prolonged treatment without control visits or an "undefined" undesirable effect (e.g.: weight gain, etc.) may cause the patient to change the rhythm and/or dosages of prescribed administration.
  - it is the pharmacist's duty to "rectify" these problems by explaining the treatment in more detail.
  - a prescription with more than three drugs prevents treatment, especially if it is for a long time.

Factors that negatively influence the level of therapeutic compliance

Factors related to patient	Deficit at cognitive level (e.g.: at comprehension or memorization)
	The association of alcoholism or drug use
	Lifestyle overloaded
	Lack of social support
	Lack of information about treatment
	The belief that the benefits of therapy are outweighed by costs
	Depression
Factors related to treatment	Complex therapeutic regimen (high number of drugs, complicated timing)
	Significant side effects of therapy
	Interference with the patient's daily routines
Factors related to the disease	Early stage of the disease (practically asymptomatic)
	Late stage of the disease (wide, obvious, recurrent symptoms despite treatment)
	Persistence of certain symptoms or signs
	Coexistence of other / other diseases
Factors related to the doctor-patient relationship	Lack of open communication with the patient
	Lack of mutual trust and respect
	Lack of attention paid to the side effects of the therapy
	Lack of supportive attitude of the doctor
	Non-compliance with confidentiality
	Lack of a warm, supportive atmosphere of the section
	Lack of facilities for the patient (transport, childcare, etc.)

The role of the pharmacist

- ✓ The pharmacist must imperatively prevent the patient from any personal initiative to modify the treatment.
- ✓ If a practical problem compromises the therapeutic plan, the patient must notify his doctor, the only one able to replace an active principle or to modify the therapeutic protocol.
- ✓ If the pharmacist identifies a risk of non-compliance, he must warn the patient that this attitude exposes him to a major uncertainty about the chances of healing, that is, it favors a severe evolution of the pathology.
- ✓ Compliance depends not only on the medicines being administered but also fundamentally on the person taking these medications, i.e. on the patient's conscious attitudes and unconscious "fantasies" about drugs and illness, on the family's attitude, of the social group to which the patient belongs in the face of illness and medicines.
- ✓ The patient is the last and most important link in achieving therapeutic success; even if the prescription is very correct, both in terms of content and form, the treatment is inefficient if the patient's compliance is not satisfactory.

- ✓ Tolerability, early improvement, ease of use - important factors that can compete for patient compliance.
- ✓ Strategies to increase compliance have great potential to reduce the costs of health care and personal suffering.

Strategies and means of action to increase compliance

Strategy	Methods of implementation
Therapeutic "training"	The patient is accustomed to the complex treatment routines, during a "training" period with placebo or other harmless products (candy, vitamins). The existence of an isomorphism between these preparations / modalities of administration (after meal, on an empty stomach, etc.) with the real medicines is sought.
Psychological counselling (individual or group)	The aim is to integrate the therapy into the regular patient program, clarify (some aspects of) the therapy for the patient, personal or telephone support provided as needed.
Mnemonics ("Technical reminders")	Medicine boxes with differentiated compartments per day/hour, detailed descriptions of the physical appearance of the drugs
Self-monitoring by the patient of compliance	Journals and records of drug ingestion, encouraging discussion with the physician of (in)voluntary deviations from the therapeutic regimen and possible reasons for them (e.g.: adverse drug reactions)
Simplification of therapeutic regimes	Build, as far as possible, a therapeutic regimen that maximizes efficiency and minimizes the number of drugs
Control, by the doctor, of the administration of the therapy ("Directed-observed therapy ")	It is especially recommended for patients with an increased risk of non-compliance (drug addicts, prison conditions, mental problems).

Practical application 4.3.

For 2 chronic patients in the pharmacy (diabetes, high blood pressure, bronchial asthma, hepatitis, etc.) develop the principles and algorithm of counseling, with the description of useful and necessary information to ensure maximum pharmacotherapeutic benefits.

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Chapter 5.

INTERACTIONS OF DRUGS.

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Considerații generale

General considerations

The drug interaction can be defined as the modificationof the action of one drug by another drug upon their simultaneous administration. This notion can be extended to interactions between drug and food constituents or environmental factors and even to interference of drug on clinical laboratory tests.

In medical practice it is necessary to take into account interactions, because patients can consult several doctors without informing about the previous recommended treatment. Most of the time, patients who are treated in an outpatient setting receive on average 4-6 preparations, and those in the hospital up to 8-10. Thus, as the number of drugs increases, the incidence rate of drug interactions increases. The most frequent and clinically significant interactions relate to anticoagulant, antihypertensive, antidiabetic, central, cytostatic and immunosuppressive drugs.

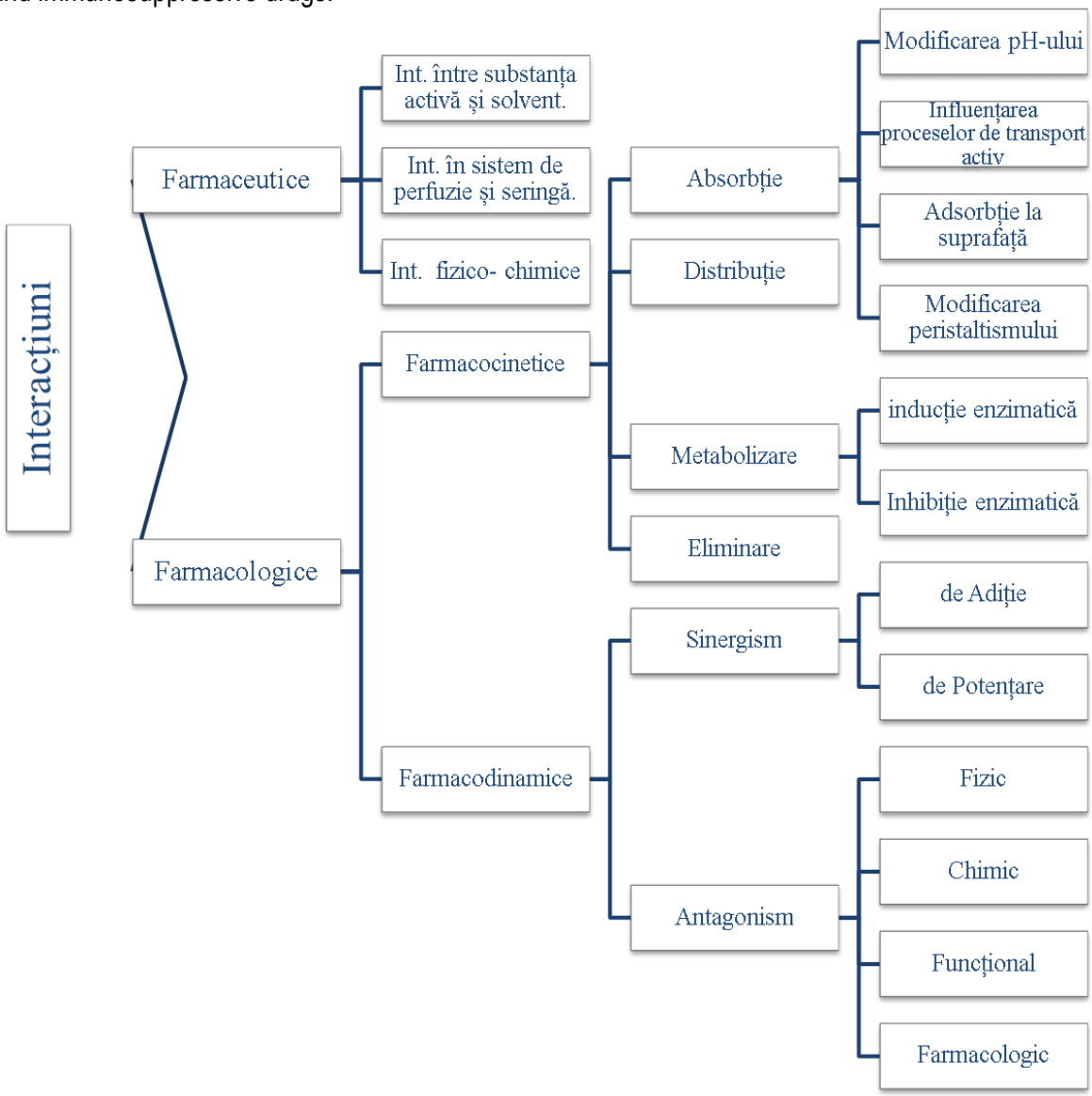

Fig. 5.1. ***Classification of drug interactions***

From the point of view of the pharmacological / pharmacotoxicological consequences it is accepted that the associations can be *advantageous* (synergistic action), or on the contrary, *disadvantageous* (not therapeutically justified). They can occur both *in vitro* and *in vivo*.

PHARMACEUTICAL INTERACTIONS (INCOMPATIBILITIES)

Pharmaceutical interactions occur prior to drug administration, usually when a drug is physically or chemically incompatible with another drug as a result of precipitation, oxidation or reduction, complexation, hydrolysis, liquefaction, effervescence, etc.

Very important are the interactions in the same syringe or infusion system. A specialist must take into account the fact that the drug substances have different physico-chemical properties, which excludes the possibility of their simultaneous introduction. From the practical point of view, two aspects of the combination therapy when introduced as injections merit attention:

- Drug interactions when introducing several solutions into an infusion system or syringe;
- Interactions between drug substances and solvent.

Solvents are used in the parenteral introduction of lyophilized powders (eg antibiotics) or in dilution of injectable preparations (corglicon, norepinephrine, strophantin K). Incorrect choice of solvent may result in drug drug uptake or precipitate formation due to incomplete dissolution. Often as a solvent, water for injections, isotonic sodium chloride solution, glucose solution or procaine solution are recommended. Each of them has its advantages and disadvantages.

Practical application 5.1.

Complete the table - with pharmaceutical interactions, according to the examples in the practice guide:

Medicine	Medicine	The mechanism of interaction	Pharmacological effects	Recomandations
Physical interactions				
Alcohol camphor solution	Boric acid solution 3%	Disruption of boric acid solubility by the non-ionized form of camphor	Reduction of antiseptic effect; the appearance of irritation	To avoid concomitant combination of these drugs
Chemical interactions				
Ferrum Lek	Tetracyclines or quinolones	Formation of insoluble complex compounds due to hydroxyl groups	Reduce the effect of antibiotics by reducing absorption	To avoid concomitant combination of these drugs
Almagel	Furosemid	Formation of the complex salt of furosemide with aluminum, without diuretic effect	Reduce the diuretic effect	To avoid concomitant combination of these drugs
Interactions of injectable medicines in the same syringe or infusion system				
Aminophylline	Bendazol	Formation of alkaline which are hard soluble in water (aminophylline possesses basic properties, therefore bendazole precipitates as a basic from salt of hydrochloride)	Inactivation of both preparations	To avoid concomitant combination of these drugs in a syringe or infusion system
Interactions of medicines with the solvent (diluent)				
Procaine hydrochloride solution for injection	Beta-lactam antibiotics	Hydrolysis and decomposition of the beta-lactam cycle	Inactivation of antibiotics	To avoid concomitant combination of these drugs in a syringe or infusion system

PHARMACOLOGICAL INTERACTIONS

Pharmacodynamic interactions

Pharmacodynamic drug interactions occur when two or more drugs are combined when we can observe the quantitative / qualitative change of the effect compared to the separate administration. Many drug interactions involve effects at the receptor level and the type of effect they produce can be synergistic or antagonistic.

In the case of *synergistic* interactions the drugs act in the same direction and the effect can be:

- ✓ addition (2 + 2 = 4) - the overall effect is the sum of the individual effects;

- ✓ enhancement (2 + 2 = 5) - the overall effect is greater than the sum of the individual effects.

Antagonistic interactions may be partial (2 + 2 = 3), when the overall antagonistic effect is less than the sum of the individual and total effects (2 + 2 = 0), when the overall effect is zero.

Competitive antagonism occurs when the two related substances are competing for the same receptor occupancy, one acting as agonist (characterized by high affinity and intrinsic activity), the second as antagonist (characterized by affinity without intrinsic activity).

Non-competitive antagonism occurs when the antagonist substance is an allosteric binding (off site of agonist binding), without blocking the receptors to compete agonist binding to the same site. The practical importance of the pharmacological antagonism (competitive or non-competitive) is expressed by the possibility of using as an antidote medication in the overdose of some substances.

Practical application 5.2.

Complete the table - with pharmacodynamic interactions:

Drug	Association	The mechanism of production	Pharmacological effects	Recommendations
Example: Aminazine	Phenobarbital	**Additive synergism.** Aminazine blocks central adrenergic and dopaminergic receptors, reducing the systemic effects of adrenaline. Pronounced sedative effect. *Phenobarbital* is an inhibitor of $GABA_A$ receptors. Sedative.	Due to the fact that operating at different target structures, the sedative effect are added up.	Dose monitoring, blood pressure, body temperature.
Cocaine	Epinephrine	**Enhancing synergism** Cocaine has local and systemic vasoconstrictor effects, inotropic, chronotropic and dromotropic positive effects. Adrenaline by acting on alpha and beta-adrenoceptors exhibit local and systemic vasoconstrictor effect.	Due to the fact that it acts at the same level, the hypertensive effect is potentiated.	Dose monitoring, blood pressure.
Atropine	Overdose of M-cholinomi-metics	**Competitive antagonism** Blocking of M-colinoreceptors	Remove the toxic effects of M-cholinomimetics	
Acetylcholine	Epinephrine	**Non-competitive antagonism** Epinephrine increases cAMP and intracellular Ca^{2+}, and acetylcholine decreases cAMP and intracellular Ca^{2+}). Acetylcholine activates G_i protein, coupled with M_2-cholinergic receptors, causes decreased intracellular cAMP (by adenylate-cyclase inhibition) and activation of K + efflux through membrane channels operated by the ligand.	Acetylcholine inhibits all the fundamental properties of the heart, except for tonotropism. Epinephrine inhibits the effects of acetylcholine by functional antagonism	To avoid concomitant administration

Pharmacokinetic interactions

The interactions of this type can occur at any pharmacokinetic stage: absorption, transport, distribution, elimination, but may, with the most important impact at the level of biotransformation (metabolic interactions).

1. At the level of absorption. Interactions affecting the oral absorption generally may be due to the following causes:

- ✓ Chemical interactions
- ✓ Alteration of gastrointestinal motility
- ✓ Change in gastric pH
- ✓ Disruption of the intestinal flora
- ✓ Other mechanisms.

2. Drug interactions at the level of drug distribution

- ✓ *Change hepatic blood flow* can have an impact on the bioavailability of heavy substances

metabolised by the liver.

- ✓ *The displacement of plasma proteins* is due to the affinity and competition of the drugs that are strongly bound to proteins to the binding sites. The displacement depends on the relative affinities of the two drugs.
- ✓ *Moving from the binding sites to the tissue* can occur in the case of drug interactions. For example, quinidine.

3. Drug interactions in the process of drug metabolism

Drug interactions involving biotransformation are the major problems in practice clinical assessment of pharmacological and adverse effects of drugs. The mechanisms of these interactions (qualitative and quantitative) concern the state of the enzymatic systems involved in their biotransformation and are classified:

- ✓ *Induction mechanism* - increasing the biotransformation of one drug by co-administration of another
- ✓ *Inhibition mechanism* by competition for substrate binding sites on the enzyme. As a result of pharmacological effects and increase the risk of toxic and dose adjustment is required (for example, phenylbutazone, some sulfonamides, cimetidine, may reduce the oxidative metabolism of phenytoin, oral anticoagulants, theophylline).

4. Drug interactions within the drug elimination process

The decrease or increase of pH may have some impact on urinary excretion of ionizable compounds with appreciable renal clearance sites.

Practical application 5.3.

Complete the table with possible pharmacokinetic interactions, according to the examples in the practice guide:

Make the copies and analyze 4 prescriptions, containing more than 3 drugs in the pharmacy, which you will evaluate through the medicines interactions based on different production mechanisms (absorption, distribution, metabolism and elimination).

Drug	Association	The mechanism of production	Pharmacological effects	Recommendations
at the level of absorption processes:				
Theophylline	Phenytoin	Reduction of phenytoin absorption	Reduction of phenytoin action	To consume the medicines in different ways
at the level of distribution processes:				
Phenylbutazone	Digoxin	Phenylbutazone substitution by digoxin in connection with proteins	Increases the concentration of digoxin in the blood plasma and increases its effect	Decreased doses of digoxin
at the level of metabolism processes:				
Fluvoxamine	Caffeine	-	Inhibition of cytochrome P450 specific isoenzyme activity	Slow fluvoxamine metabolism with increased blood concentration and possibility of developing toxic effects
at the level of elimination processes:				
Paracetamol	Methotrexate	Paracetamol inhibits tubular secretion of methotrexate	Increased methotrexate toxicity	To avoid associations

OTHER TYPES OF INTERACTIONS

Interactions between drugs and plant products.

The natural treatment is highly appreciated by the chronic patients. Since the use of plant products is a tradition, their management is done without prior consultation with the doctor. The role of the pharmacist is to inform patients to prevent these interactions.

Many people live with the wrong impression that being natural, all plants and foods are safe. It's not like that ! Often, plants and foods interact with medications normally administered resulting in serious side effects.

Experts say that natural does not mean completely safe. All you ingest can interact with something else. Drugs taken orally in the digestive system go the same way with all plants and food taken orally. So, when a drug is mixed with any food or any medicinal plant, each of them can affect how the body metabolizes them.

Some drugs affect the body's ability to absorb nutrients. Similarly, some plants and foods may decrease or increase the impact of drugs.

Theophylline, a medicine used to treat asthma, contains xanthine, which is found in tea, coffee, chocolate or other sources of caffeine. High consumption of these products while taking Theophylline increases its toxicity.

Certain vitamins and minerals also have an impact on the medication. Large quantities of broccoli, spinach or green leafy vegetables rich in vitamin K, which help to clot blood, can counteract the effects of medicines given precisely to prevent coagulation.

As people discover new herbs, there is a growing possibility that they will abuse them, ending up with great problems. Patients such as the elderly, patients taking 2 - 3 medications for chronic conditions, diabetes, hypertension, antidepressants, high cholesterol, heart problems, are the first to be protected from these side effects.

We present below some of the interactions between herbs and drugs.

The hawthorn (gherghin), which is advertised as being effective in reducing angina attacks by lowering blood pressure and cholesterol levels, should never be taken with Lanoxin (Digoxin), a drug prescribed for most heart problems. The combination can slow the heart rate too much, causing heart attacks.

Ginseng, according to research, may increase blood pressure, being dangerous for those who want to keep it under control. Ginseng, garlic or ginger supplements, when taken with blood thinning medicines, can cause bleeding. In rare cases, ginseng can cause insomnia. Consumption of caffeine and ginseng simultaneously increases the risk of over-stimulation and causes discomfort at the gastrointestinal level. Also, consuming a longer period can cause menstrual disorders and breast sensitivity in some women. Ginseng is not recommended for pregnant women or breastfeeding mothers.

Garlic capsules combined with medications for diabetes can cause a dangerous drop in blood sugar. People who are sensitive to garlic may experience heartburn and gas burns. Garlic has properties that prevent coagulation. Thus, a doctor should be consulted if already taking anticoagulants.

Soft grass (*Chrysanthemum parthenium*), considered to be the natural remedy for migraines and headaches, should not be taken with other migraine medicines. Heart rate and blood pressure will rise to dangerous levels.

White willow, a plant used against fever, headache, rheumatic problems, can cause gastrointestinal irritation if used long. It has the same reaction as aspirin (aspirin is a derivative of white wicker). Long-term use can lead to ulcers.

Drug-food interactions

Drug-food interactions are today the cause of multiple therapeutic failures, especially in the case of polymedication. Because, most often, the mechanism of interaction is unclear, it becomes quite difficult to anticipate a possible interaction between consumed foods and peroral drug forms. For example, antibiotics such as tetracycline, doxycycline, ciprofloxacin and norfloxacin interact with products containing calcium (eg milk), iron or magnesium, minerals that we find not only in diet, but also in supplements with multivitamins and minerals. In order to avoid these interactions that lead to a decrease in the effectiveness of the antibacterial treatment it is recommended to administer them at a distance of at least 2 hours.

Furazolidone, an antidiarrheal, anti-inflammatory and intestinal anti-infectious agent, interacts with foods containing tyramine such as fermented cheeses (parmesan, gorgonzola), smoked meat, soy, alcohol and can lead to hypertensive crisis, headaches or palpitations. In these cases it is recommended to avoid the concomitant use and 4 days after finishing the furazolidone treatment. Grapefruit juice contains substances that inhibit the enzyme responsible for metabolizing many drugs in the liver and thus increase the concentration of drugs in the blood and can lead to adverse reactions. Some examples of drugs that interact with grapefruit juice are: hypocholesterolemiants (atorvastatin), benzodiazepines (diazepam, alprazolam), calcium channel blockers (diltiazem, verapamil), anticonvulsants (carbamazepine), antibiotics (clarithromycin), erythromycin. Corticosteroids (eg: prednisolone), the class of anti-inflammatory, antiallergic

and immunosuppressive drugs, interact with sodium-containing foods such as cooking salt, mineral water, commercial spices (Vegeta) and can increase blood pressure, salt and water retention, resulting in edema (swelling of the lower limbs), increased potassium excretion. It is recommended to avoid excessive salt consumption.

Interactions between nutritional supplements and medicines often lead to loss of therapeutic efficacy and / or increased toxicity. A good understanding of the mechanisms of interaction between drugs and plants active principles is essential for the clinical risk assessment and is vital for health practitioners (physicians, pharmacists) to ensure that the use of the plants is safe for the patient. Despite their widespread use, the risks of combining nutritional supplements with medicines are difficult for consumers to understand, as they are guided by the premise that what is natural is safe.

A major challenge for healthcare providers in advising patients on nutritional supplements is that the clinical evidence for interactions between medications and nutritional supplements can be ambiguous and sometimes contradictory. Also, there are often barriers in practice to identify evidence of drug - nutritional supplement interactions.

The evidence available to guide practitioners in decision making is complex and consists of a number of sources, including spontaneous case reports or in vivo studies on drug interactions in healthy subjects and patients. In the absence of further rigorous studies to assess the clinical significance of interactions between drugs and medicinal plants, an evidence-based assessment of the current literature is essential to guide practitioners involved in patient care.

Both patients and physicians need to be educated on the clinical significance of interactions between drugs and medicinal plants.

Practical application 5.4.

Complete the possible interactions with plant-derived products (PV), food, alcohol, tobacco according to the examples in the practice guide: 2 examples of each

Drug	The association	The mechanism of interaction	Pharmacological effects	Recomandations
Plants				
Digoxin	Tutsan	Pharmacokinetic interaction by induction of P glycoprotein	Reduction of maximal digoxin concentration in blood	To increase the dose of digoxin or avoid co-administration
Food				
Levodopa	Vitamin B6-rich products (grasses, meat)	In the body, vitamin B6 after phosphorylation is converted to pyridoxalphosphate and participates in the metabolism of amino acids and the conversion of levodope to dopamine.	Reduces levodopa effect	To avoid concomitant administration
Clonidine	**Alcohol**	Alcohol potentiates the hypotensive action of clonidine	Developes collapse	To avoid alcohol consumption
Propranolol	**Tabacco**	Hidrocarburile aromatice policiclice ale fumului de tutun, fiind inductori ai izoenzimelor citocromului P 450 1A2 (în ficat) duce la intensificarea metabolismului propranololului Polycyclic aromatic hydrocarbons of smoke tobacco, being inducers of cytochrome P 450 1A2 (in liver) isoenzymes, leads to intensification of propranolol metabolism	Reduces the concentration of propranolol in the blood and respectively decreases its action	To avoid smoking

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Chapter 6.

PHARMACEUTICAL ASSISTANCE AND PHARMACOVIGENCE ACTIVITY.

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In the drug delivery activity, students will be based on the principles of pharmaceutical care practice and the rules of good pharmaceutical practice.

Pharmaceutical assistance (Pharmaceutical care) is the responsible assurance of drug therapy in order to obtain results that improve the quality of life of the patient. The results are:

1) the cure of the disease,
2) elimination or improvement of symptoms,
3) stopping or slowing down the disease process,
4) prevention of diseases or symptoms.

The most important in the practice of pharmaceutical assistance is the patient, the pharmacist assuming responsibility for problems related to his drug therapy. It represents a systematic and exhaustive process, in which the pharmacist's role is:

1) identification of problems related to drugs (real and potential) in the patient.
2) solving the real problems related to drugs,
3) prevention of potential problems.

It is necessary for the pharmacist to collaborate with the patient and the health care providers to promote health, to prevent disease, to initiate, evaluate, monitor and modify the therapy in order to ensure a safe and effective therapeutic regimen for the patient.

The pharmacist in general, but also the clinician pharmacist, are not professionally trained to perform the clinical examination of the patient and to diagnose the disease. On the other hand, the sources and methods of information of the pharmacist in the community pharmacy, regarding the patient's illness, are reduced and the time allowed for information is relatively short. Therefore, the task of the pharmacist to perform a minimal consultation in the community pharmacy, when the patient presents the manifestations of disease and asks for the recommendation of an OTC medication, is as responsible for human health, as difficult.

The incomplete information sources and methods available, as well as the reduced qualification, allow the pharmacist to present only a diagnostic hypothesis. This diagnostic hypothesis is absolutely necessary in order to be able to advance the initial decision (to refer directly to the doctor or to recommend a first-line pharmacotherapy with OTC medicines, accompanied by the advice of presenting to the doctor if the suffering continues).

The sources of information of the pharmacist in the community pharmacy present:

- ✓ *the patient (anamnesis and observation of the patient);*
- ✓ *the belongings (parents, family, relatives, friends, colleagues);*
- ✓ *epidemiological data (ongoing epidemics, etc.).*

The patient is the main source of information. The methods of information of the pharmacist, in the community pharmacy:

- ✓ *anamnesis (listening and interviewing the patient);*
- ✓ *patient observation (general appearance, face, eyes, skin); possibly measuring the temperature, pulse, BP.*

Anamnesis

Anamnesis, based on listening and interviewing (conducted dialogue) with the patient, provides information on:

- ✓ symptoms (I am cold; I have the flu; I have a runny nose; I cough; I have fever; I have headache; I have back pain; I have chest pain; I have abdominal pain; I have intestinal colic; I am constipated; I have diarrhea, etc.);
- ✓ objective (rhinorrhea, cough, fever etc.) and subjective symptoms (headache, colic, constipation, diarrhea, pain, etc.);
- ✓ the onset, the evolution, the intensity and the particularities of the symptoms;
- ✓ the history of the symptoms (periodicity, frequency, duration, acute, chronic);
- ✓ personal and collateral (family) history;
- ✓ presentation to the doctor (currently and/or in previous episodes);
- ✓ a possible diagnosis made by the doctor (currently or in a previous episode);
- ✓ any previous treatments and their effect (medication history);
- ✓ chronic diseases and ongoing pharmacotherapy;

✓ ongoing self-medication;
✓ nutrition, alcohol consumption (occasional, chronic), smoking, drugs;
✓ stress.

Symptoms may provide indices for the disease diagnosis hypothesis. It should not be overlooked that the same symptom manifests in a variety of diseases, some of which are particularly serious, which could endanger the patient's life, in the event that the healthcare is delayed. Therefore, it is very important to know the correlation between the symptoms and the diseases in which they may occur.

The peculiarities of the symptom (the characteristics and the circumstances in which it appears) can narrow the area of possible diseases. Example: dizziness when suddenly getting out of bed, suggests orthostatic hypertension; violence, which occurs in access is characteristic of Meniere syndrome; at the movement of the head, it may provide an indication of cervical spondylosis or brain tumor.

In the diseases in which a symptom is presented, only in some cases can the pharmacist intervene, with first-line pharmacotherapy for 1-2 days. In other cases, the pharmacist is obliged to refer the patient to the doctor, giving him a symptomatic OTC product, strictly for 1-2 doses.

Example: In headache, the pharmacist may recommend an OTC analgesic product for 1-2 days, only if the diagnostic hypothesis competes with the following diseases: migraine, asthenic neurosis, cervical spondylosis; In case of other disoders (high blood pressure, vision disorders, brain tumors), the pharmacist recommends that the patient consult the doctor.

Observation of the patient

The patient's observation (general appearance, face, eyes, skin), made directly by the pharmacist, is important for the detection:

• objective symptoms (rhinorrhea, cough, fever, etc.);
• signs of disease (color of face, eye, skin; chills, etc.).

A sign can be found in a number of diseases, because there are no specific signs for a disease (pathognomonic signs). As a result, it is necessary to know the correlation between the signs and the diseases in which they may occur.

Problems related to drug therapy, which the pharmacist must solve, can have different causes:

✓ Need for additional therapy:
• The patient has a new health problem, which requires treatment.
• The patient has a chronic disease, requiring continued therapy.
• It is necessary to add a new drug to the therapeutic scheme, with synergistic or potentiating effect.
• Prophylactic treatment is required.
✓ *Use of useless drugs:*
• *The patient uses medicines, without a justified indication.*
• *Accidental or intentional intoxication, which determined the patient's current state.*
• *Problems are caused by the abuse of alcohol, tobacco, drugs (although they are not drugs, from the point of view of pharmaceutical assistance, they can be included in this category)*
• *The disease can be treated non-medicinally.*
• *The patient uses polytherapy, although monotherapy is sufficient.*
• *The patient uses medicines to relieve the adverse effects of other drugs used.*
✓ *Wrong drug choice:*
• *The recommended (or used) drug is not effective in the patient's condition.*
• *The patient is allergic to the recommended drug.*
• *The patient presents risk factors, which contraindicates the drug (pregnancy, lactation, renal, liver, other related diseases, etc.).*
• *The patient was recommended an effective medicine, but the cost is too high.*
• *The recommended drug is effective, but not safe (side effects, contraindications, interactions).*
• *The microorganism that caused the infection is resistant to the antibiotic recommended to the patient.*
✓ *Doses too small:*
• *The recommended dose is too low to achieve the expected effect.*
• *The plasma concentrations of the drug are lower than the lower limit of the therapeutic domain.*
• *The antibiotic for prophylaxis prior to surgery was administered too quickly.*
• *The route of administration or the pharmaceutical formulation does not provide the desired effect, the dosage range*

is not appropriate (ex.: analgesic administered "as needed").

✓ *Doses too high:*

• *Doses too high for the pathophysiological state of the patient (ex.: elderly, children, renal or hepatic impairment, etc.).*

• *The plasma concentrations of the drug are higher than the upper limit of the therapeutic domain).*

• *The doses of the drug were increased too quickly.*

• *Improper replacement of the drug, dose, route of administration, pharmaceutical formulation.*

• *Improper dosing range.*

✓ *Adverse effects:*

• *Drug administered i.v. too fast.*

• *Allergic reaction of the drug.*

• *The patient has contraindications for the administration of a drug (risk factors that could cause adverse reactions). Idiosyncratic reaction to the drug.*

• *The bioavailability of the drug is impaired due to interaction with another drug or food.*

• *The effect of the drug is modified as a result of the enzyme inhibition or induction produced by another concomitant drug.*

• *The effect of the drug is modified as a result of the displacement of plasma proteins by another co-administered drug*

• *The effect of the drug is modified by the food additives from the foods consumed by the patient.*

• *The results of some laboratory tests are influenced by the drugs administration.*

✓ *Compliance with drug therapy:*

• *The patient did not use the appropriate medicine due to an error (prescription, release, administration, monitoring).*

• *The patient did not follow the recommendations on how to use the medicine.*

• *The patient did not use the recommended drug due to the high price.*

• *The patient did not use the drug because he did not understand the instructions.*

• *The patient did not use the medicine because it contradicts his opinion.*

The principles of pharmaceutical care practice have been adopted by the American Pharmaceutical Association (APhA) - Pharmaceutical Care Guidelines Advisory Committee (1995) and Council of the International Pharmaceutical Federation (FIP) (1998). These are:

1. Collecting patient data

✓ through discussion with the patient, his/ her representative or the doctor requires the prior informed consent of the patient; requires compliance with the law and confidentiality.

✓ the data are recorded in the patient's pharmaceutical file.

2. Evaluation of the information obtained

✓ the pharmacist, in collaboration with other health care providers, identifies and evaluates the most appropriate attitude to ensure effective, safe and cost-effective therapy and to minimize current or potential health problems;

✓ the conclusions are recorded in the patient's pharmaceutical file.

3. Formulate a plan

✓ the plan is elaborated in order to solve the identified problems;

✓ is developed in collaboration with the patient and, if necessary, with the doctor or other health professionals and may include:

- protocol for initiating drug/non-drug therapy or for modifying the previous one,
- development of mechanisms to monitor the therapy,
- guiding the patient to an appropriate source of health care, the pharmacist records the plan and the desired results in the patient's pharmaceutical file.

4. Implementation of the plan

✓ is carried out in collaboration with the patient to ensure the complete understanding of the plan by him and his involvement in the therapeutic plan; and may include:

- contacting the doctor to clarify or change the prescription, initiation of therapy,
- educating the patient and/or the caregiver,
- release of drugs and/or other necessary products,
- establishing the monitoring modalities,

- coordinating the meetings with the other healthcare providers to whom the patient is sent.
  If applicable, the elements of the plan are also communicated to the other health care providers.
  Monitoring and modifying the plan to ensure positive results

✓ the pharmacist regularly evaluates, together with the patient, the progress made in order to achieve the desired results; the evaluation is based on the objective and subjective parameters of monitoring established; the progress achieved is communicated to the patient to encourage him/her to continue working;

✓ if the expected progress is not achieved, the plan must be modified, applying the principles used in the elaboration of the initial plan;

✓ the pharmacist provides to the other professionals involved in providing medical care, the patient, information on the patient's adherence to the therapeutic plan; the pharmacist records the progress made in the patient's pharmaceutical file.

Model form for pharmaceutical assistance - allows the recording of patient data, of the problems related to the therapy identified by the pharmacist and of the measures recommended by the pharmacist. It can be used in the elaboration of the patient's pharmaceutical file. The information will be obtained with the consent of the patient, the patient, his representative or the doctor. Helpful questions can be used to obtain the most complete information. If applicable, the problems identified and the measures (plan) recommended by the pharmacist will be communicated to the doctor.

Practical application 6.1.

Complete 2 forms of pharmaceutical assistance of patient in the hospital of the pharmacy where you practice. The patient will be followed for 3 months, in case of the community pharmacy or during the hospitalization, in case of the hospital pharmacy. Update patient data for each disease. Introduce the information obtained from the patient and your observations in the form below:

1. GENERAL INFORMATION ABOUT THE PATIENT

Name: ..... First name:.....
Age: ..... years Height: m
BMI:..... ..... kg/m^2
Gender: M F Body weight: ..... kg
Occupation: ..... ……
Pathophysiological condition (pregnancy, elderly, renal, liver, associated diseases): ……
.....
.....
Physical or other disability (eg paralyzed, blind, illiterate, etc.):.....

2. ALLERGIES

Helpful questions:

Are you allergic to medicines, foods, environmental factors, etc.? ……
If YES, how does this allergy manifest?..... ……
Did the reaction occur immediately or after a certain time (depending on how many doses of medicine)?.....……
Are there any other allergic people in the family?……..

3. MEDICAL HISTORY (current history and conditions of the patient or family)

Current diseases: ....
Personal medical history: ....
Family medical history: ....

4. LABORATORY TESTS, OTHER EXAMINATIONS

Parameter/Date	RBC …….....
Hemoglobin	Hematocrit ……...
Leukocytes.....	Platelets ……..
Na^+	K^+……
Ca^{2+}	Urea ……...
Serum creatinine	AST ……
ALT.....	Total bilirubin ……...
Glucose.....	Total cholesterol ……

LDL-col ..... Triglycerides ……
Blood pressure..... Pulse……..

5. SUPPORTING QUESTIONS:

You get used to:

- o black / green tea .....daily quantity ……..
- o coffee.....daily quantity ……
- o alcohol, type of drink.....daily quantity.....
- o favorite foods.....daily quantity ……

Do you smoke? How long, how long?.....

Do you follow a certain diet (no salt, no fat, no sugar, etc.)? If yes, what is the regime? ……

.....

6. DRUGS PRESCRIBED BY DOCTOR

Trade name, DCI, concentration	Dosage	Duration of therapy		Reason for use (diagnosis)	Effectiveness	Adverse reactions
		Start date	Stop date			
Ex. Doxycycline, capsules	*100 mg 2 times/day for 10 days*	*22.03.2019*	*02.04.2019*	*Chronic pyelonephritis in the acute phase*	*The preparation was effective. The subjective symptoms are gone. The data was normalized.*	Nausea, anorexia, symptoms of Candida superinfection

7. COMPLIANCE WITH TREATMENT

Helpful questions:

- Have you been informed about the treatment you should take?

YES NO

- Have you been advised about the way you should use the drugs?

YES NO

- Who gave you the information about:

✓ purpose of treatment

DOCTOR
PHARMACIST

✓ the correct way to use drugs

DOCTOR PHARMACIST

Consider that the drugs are doing you good? YES NO

You have never been prescribed drugs? ……

If yes

✓ How often? ……..

✓ why (there are too many, you simply forgot, they had adverse effects, they were not efficient, the cost is too high, etc.)? ……

PROBLEMS RELATED TO DRUG THERAPY

Date	Problem	Cause	Pharmacist intervention to prevent or solve the problem
Example:			
17.03.2013	Manifestation of adverse reactions of the drug used. Urticaria at intramuscular administration of benzylpenicillin.	*Individual intolerance to penicillin and lack of penicillin skin sample.*	*Patient counseling for stopping drug administration and recommending antihistamines.*

PHARMACOVIGENCE ACTIVITY

Objectives

In the practice activity at the pharmacy students will seek to deepen their knowledge on the adverse reactions, which may occur following the use of essential drugs and on how to report them, according to the file prepared by the Medicines and Medical Devices Agency.

Useful definitions

Pharmacovigilance is defined as the entire activity of detecting, evaluating, validating and preventing adverse reactions to medicinal products.

Adverse reactions are harmful, always undesirable, reactions that occur after the administration of a drug at commonly used doses for prophylactic, curative or diagnostic purposes.

Serious adverse reaction is defined as an unwanted reaction related to the use of a drug that ends in death, leads to prolonged hospitalization, infirmity or congenital malformations. Their reporting is mandatory. The efficacy and safety of a drug are demonstrated from the pre-authorization phase in clinical trials.

The spontaneous reporting system consists of reporting suspected adverse reactions during clinical practice.

Who reports?

- ✓ Health professionals (doctors, dentists, pharmacists, nurses)
- ✓ Pharmaceutical companies
- ✓ Patients

The reactions are collected and analyzed by the Medicines and Medical Devices Agency. After analyzing these reports, a signal can be generated that can lead to:

- ✓ warnings about that medicine
- ✓ limitations of use
- ✓ even upon his withdrawal from the market.

Where is it reported?

At the Medicines and Medical Devices Agency on the Card for spontaneous reporting of adverse reactions - return of completed form by post, fax or e-mail.

How do we detect an Adverse effect (AE)?

Detecting an adverse reaction is part of the process of establishing a patient's diagnosis. If the patient is under treatment with drugs, the differential diagnosis, the possibility of an adverse reaction should be considered.

For this purpose:

- ✓ Must know all the drugs a patient takes, including OTCs, long-term drugs or natural supplements;
- ✓ It must be determined whether the event described by the patient is due to a drug (or several drugs in therapy) or to the patient's state.

Criteria that help us recognize an adverse reaction (AR):

- ✓ The temporal relationship between medicine administration and the occurrence of AR
- ✓ Nature of AR
- ✓ Investigations carried out

Temporary relationship

- ✓ Has the reaction occurred or worsened when the drug reached the maximum plasma concentration or when the dose was increased?
- ✓ Has the reaction improved or disappeared when the dose of the drug was lowered, or the drug withdrawn?
- ✓ If a drug interaction is suspected, the time of introduction of the drug that could interact, is it related to the time of RA?
- ✓ If an allergic reaction is suspected, did the patient have previous contact with the suspected drug?

The lack of previous exposure does not exclude the possibility of an allergic reaction, but the previous exposure is conclusive for such a case.

Grade I hypersensitivity reactions: (pruritus, hives, angioedema, bronchospasm, anaphylaxis) - usually occur at the second exposure, a few minutes after administration up to 2 hours, the most commonly responsible drugs being aspirin, opioids, penicillins, some vaccines etc.

Increased attention to the cross-reactivity of the following drug compounds:

- ✓ Beta-lactam antibacterial: amoxicillin, cephalosporins, carbapenems
- ✓ Sulphonamide class: sulfamethoxazole and sulfasalazine
- ✓ Lidocaine with mepivacaine
- If it is a congenital anomaly, the exposure to the drug took place during the gestation period what can justify the anomaly?
- If it is a tumour, has it been long enough for the tumour to develop?

The type of adverse reaction should be considered:

- Immediate AR (hypotension on calcium channel antagonists) - the time to be evaluated is the time that elapsed between the last dose administered and the time of reaction onset.
- Delayed AR (cataract to corticosteroids, hepatotoxicity to methotrexate) The relevant period is the time between the start of therapy and the time of reaction onset.

Nature of adverse reactions.

The frequency of the described event and the level of its association with the drugs.

- headaches are common, their association with medicines may be accidental
- aplastic anaemia has a low incidence, but is often associated with the use of certain drugs (carbamazepine, phenytoin, chloramphenicol, co-trimoxazole, chlorpromazine, carbimazole)

The investigations carried out.

- determining the plasma concentrations of the drug,
- biopsy,
- allergic tests,
- determining the impairment of certain functions (renal, hepatic, thyroid),
- the patient's re-exposure to the suspected drug.

These investigations:

- ✓ can help to establish a diagnosis and to monitor the patient after making modifications of the therapy
- ✓ may exclude other alternative diagnoses

Type A reactions

- respond to dose reduction or temporary discontinuation of therapy if necessary (severe or serious adverse reaction).
- Exception: permanent AR (pulmonary fibrosis with amiodarone) - withdrawal of the drug as soon as the disease is recognized can reduce the magnitude of the toxicity.

Type B side effects

- rapid quick actions are necessary and important due to gravity.
- urgent treatment and temporary withdrawal of all medicines are required, with the subsequent reintroduction of the essential drugs under strict supervision.

For withdrawal of medicines if they are essential to the patient

It must be evaluated:

- ✓ the indispensability of the drug administration ↔ the possibility of replacing it with another therapeutic agent with the same effectiveness but with low risk of developing AR
- ✓ severity of adverse reaction
- ✓ the possibility of treating it.

The patient should be monitored during withdrawal of the drug.

- ✓ The period needed to improve the symptoms associated with AR varies according to the rate of drug elimination and pathology

When AR signs disappear and the patient feels better, they can enter / reintroduce under observation:

- ✓ a drug related pharmacologically to the suspected drug in the onset of AR
- ✓ the suspected drug, if it is essential for the patient, but in lower doses (in case of dose-dependent reactions).

Causality of AR

In establishing the causal relationship, it is evaluated:

- ✓ the time of onset of the adverse reaction,
- ✓ differential diagnosis (which excludes other causes),
- ✓ the incriminated drug is identified based on pharmacological plausibility or by excluding other drugs,

- ✓ effect on withdrawal of the drug,
- ✓ the effect of a possible re-exposure.

Can the drug cause this side effect in general?

- information available in the summary of product characteristics / literature on observed cases
- the fact that the adverse reaction can be observed in some patients and not others, depends on the presence of risk factors

Did the drug cause an adverse reaction to this patient?

- the data and information available in a specific case
- the experience of the person who performs the causality assessment

What is the minimum amount of information required to report an adverse reaction?

- an identifiable (medical qualified) rapporteur: names, contact details - telephone, qualification
- an identifiable patient: initials, patient number, date of birth, age, decade of age or sex
- at least one suspected medicine or active substance
- at least one suspected adverse reaction.

What is the essential information for evaluating causality?

- Suspected drug/medicine (product series)
- Mode of administration (dose, frequency and route of administration, duration of treatment)
- Previous drug use - the effect?
- Detailed description of AR (signs, symptoms, laboratory data)
- ▸ Date of AR appearance / date of disappearance of AR / duration of AR
- Treatment discontinuation / dose reduction - the effect?
- Reintroduction of the suspected drug/medicine (rechallenge) - recurrence of AR?
- Treatment of AR
- Evolution of the patient - the sequelae?
- Concomitant therapy
- Other relevant information about the patient (pathology, history, known allergies).

Causality according to WHO categories

AR	Temporary relationship	Alternative causes (patient's disease / associated medications)
Certain	▪ The plausible relationship between drug administration and the occurrence of the event ▪ Plausible withdrawal response (pharmacological, pathological) ▪ Pharmacological/phenomenological explanatory event ▪ Positive response to re-exposure	AR cannot be explained by the patient's illnesses or other medications
Probable/Likely	▪ The relationship between drug administration and the occurrence of the event - reasonable ▪ Reasonable withdrawal response ▪ Re-exposure is not required	It is unlikely to be explained by the patient's condition or other medications
Possible	▪ The relationship between drug administration and the occurrence of the event - reasonable ▪ Information on the effect on withdrawal of the drug is non-existent or unclear	It can be explained by the patient's condition or other medications
Unlikely	▪ Unlikely (but not impossible) temporal relationship	Patient's illnesses or other medications are plausible explanations

Causality according to the Naranjo algorithm

Criteria	Yes	Not	It is not known
1. Are there any conclusive reports on this AR?			
2. Did AR appear after the administration of the suspected drug?			
3. Did AR disappear at the withdrawal of the suspected drug or was a specific antagonist given?			
4. Has AR reappeared?			

5. There are alternative causes that could determine the occurrence of AR			
6. Has AR appeared again on placebo?			
7. Was the drug detected in blood or other fluids at concentrations that could be toxic?			
8. Was AR more severe when the dose was increased or less severe when the dose was lowered?			
9. Has the patient ever experienced a similar adverse reaction to the same or similar drug to a previous exposure?			
10. Has the adverse event been confirmed by objective evidence?			

Causality according to the modified Karch-Lasagna algorithm

	Adverse reaction category			
Criteria	**Secure**	**Probable**	**Possible**	**Relative**
Temporary relationship	Yes	Yes	Yes	Yes
Known AR	Yes	Yes	Yes	No
The existence of an alternative cause	No	No	Yes	No
Improvement upon withdrawal of the drug	Yes	Yes	Yes or No	Yes or No
Recurrence at re-exposure	Yes	(-)	(-)	(-)

(-) - no information

Practical application 6.2.

Fill an adverse reaction report sheet of side effects (adverse reaction) which you identified in a patient during the internship, according to the reporting sheet prepared by the Agency of Medicines and Medical Devices (Annex II). The file can be obtained from the website of the Agency of Medicines and Medical Devices.

COMMUNICATION FORM
ABOUT THE ADVERSE REACTIONS OF MEDICINAL PRODUCTS AND OTHER PHARMACEUTICALS
(will be underlined the variant of the accepted answer)

Example.

1. **The medical institution.** *IMSP Clinical Hospital of MoH*
   Address. *Chisinau, 51 A. Pushkin Street.*
2. **The service (department)**. *Cardiology*
3. **The doctor who recorded the adverse reaction.** *Tofan Alexander.* **Phone** *022234456*
4. **The patient (name, surname)**. *Petrachi Ion.* **Nr. sheet of observation.** *22*

Date of admission. *15.02.013* **Date of discharge (for patients discharged)** *02/23/2013.*

5. **Clinical diagnosis (basic, concomitant, complications):** *Hypertension, medium severity (Grade II). Ischemic heart disease.*

Anamnesis:

The patient has been suffering from ischemic heart disease since 2005, when the retrosternal pain abolished with nitro-glycerine administered sublingually appeared. Periodically the patient went to the doctor and after his treatment his condition improved, but for 1 year the patient's condition worsened with the intensification and increase of the frequency of the retrosternal pain and the increase of blood pressure values. To reduce blood pressure the patient used metoprolol tablets. As his condition worsened, the last 2 weeks he started treatment with Enalapril recommended by the family doctor, after which he had dyspnoea with coughing attacks, sometimes bloody. The lack of efficiency of the treatment administered at home and the aggravation of the condition made him to go to the doctor with the hospital admission.

6. **Age** *55 years* **Body weight** *80 kg* **Gender: M □ F □**
7. **Ethnicity of the patients: Caucasian □ Negroid □ Mongolian □ Asian □ Arabic □**
8. **Onset of adverse drug effect:** *01.02.2013* **(date, month, year)**
9. **End date of adverse effect (if known):** *17.02.2013*

10. Description of the adverse effect on the drug (or a certain combination of medicines) - onset, localization, symptoms: The patient shows dry coughing and respiratory disorders after administration of Enalapril which has been used for 2 weeks.

Severity of adverse effect: Mild □ Medium θ Serious □

11. Evolution of the adverse effect:

- ❑ Healing without sequelae (consequences);
- ❑ Healing with sequelae (consequences);
- ❑ In process of development;
- ❑ Death of the patient as a result of drug administration;
- ❑ Death - the drug may have contributed to it, or the drug possibly caused the death;
- ❑ Death - it is not related to the administration of the drug;
- ❑ Death - the cause of death is not clear.

12. The drug (or medicines, drug combinations) suspected of having an adverse effect:

Product name, pharmaceutical form, manufacturer, country, preparation series with manufacturing date	**Dose at one administration**	**Nictemeral dose**	**Frequency (Periodicity) administration**	**Route of administration**	**Beginning of administration of preparation (day/month/ year)**	**Finishing administration of preparation (day / month / year)**	**Illness or the pathological process, which served as a right indication for administration of the preparation**
					When the data is not known exact, will be indicated the term of administration of the preparation until the onset of adverse effect		
ENALAPRIL 5 mg, tablets, SC Terapia SA, Romania, NO. 6742/2006/01, 05.09.2006	*5 mg*	*10 mg*	*Two weeks, 4 times a year*	*Oral*	*01/02/2013*	*02/17/2013*	*High blood pressure*

The abolishment of the preparation was followed by regression the adverse effect?	**Yes** / **No** / Does not know	Was it repeated or aggravated by the adverse effect upon repeated administration of the preparation?	**YES** / **NO** / It is not known

Appreciate the role of the suspected preparation (or preparations) in the occurrence of the adverse effect:

- ❑ definitely/sure (sure adverse reaction)
- ❑ likely (probable adverse reaction)
- ❑ possible (possible adverse reaction)
- ❑ less likely/doubtful (improbable adverse reaction)
- ❑ conditioned/unclassified (adverse reaction conditioned/unclassified)
- ❑ non-classifiable/non-evaluable (non-evaluable/non-classifiable adverse reaction)
- ❑ the interaction between 2 or more drug preparations is suspected in the adverse effect

13. Concomitant medication (the preparations that have been indicated for the correction of the adverse effect will not be listed):

Product name, pharmaceutical form, manufacturer, country, preparation series with manufacturing date	**Dose at one administration**	**Nictemeral dose**	**Frequency (Periodicity) administration**	**Route of administration**	**Beginning of administration of preparation (day/month/year)**	**Finishing administration of preparation (day / month / year)**	**Illness or the pathological process, which served as a right indication for administration of the preparation**
					When the data is not known exact, will be indicated the term of administration of the preparation until the onset of adverse effect		

Nitroglycerin 0.5 mg, sublingual tablets, SC Zentiva SA, Romania, Nr. 142/2007/01, May 07, 2007	*0.5 mg*	*0.5 mg*	*1 daily, for 5 days*	*Sublingual*	*02.10.2013 / 15.02.2013*	*Ischemic heart disease*

14. Data from anamnesis (diseases, allergic conditions, drug allergy in the past, problems of kidney or liver disease, pregnancy, lactation, special diets, harmful habits, exposure to radiation ionizing etc.)

The patient has been suffering from ischemic heart disease since 2005, when the retrosternal pain abolished with nitroglycerine administered sublingually appeared. Since 2012, medium-high blood pressure has been established. Other concomitant diseases do not have. Allergic conditions or allergic reactions to medicines till now not manifested. He smokes 1 pack of cigarettes per day.

15. Measures to correct the adverse effect:

- ❑ Cancelling the drug preparation
- ❑ Reduction of the dose of the drug preparation
- ❑ Additional drug therapy to relieve the adverse effects, list the measures taken and the medicines administered: ……
  ……
- ❑ Without correction
  .....
- ❑ Cancellation of concomitant therapy (indicate which medicines were cancelled): ……

16. Additional data on the adverse effect (clinical, laboratory, the concentration of drug in the blood and tissues, necropsy data in the case of death of the patient). Describe the pathological changes, indicating in norm brackets:

The additional data for the detection of the adverse effect have not been made.

17. Other information on the medicinal product suspected of having an adverse effect or on the adverse effect:

- ❑ Has the patient received this drug before? Yes □ **No** □ Not known □
- ❑ Did the patient present identical or different reactions to this product? Yes □ **No** □ Not known □

If so, indicate what kind of reaction? ……

- ❑ Has the patient experienced similar adverse reactions to other drugs? Yes □ **No** □ Not known □
  If Yes, then to what drugs did these reactions occur: ……
- ❑ Did the patient have similar side effects, which were not caused by the administration of drugs? Yes □ **No** □ Not known □
- ❑ Have been really other factors may influence the occurrence and development of the adverse effect described (chronic diseases of the system, the dependence of drug, environmental factors, radiation ionizing, use of substances toxic chemicals, allergy)? Yes □ **No** □ Not known □

If Yes, then list: ……

18. Statute of the preparation:

□ Preparation authorized in the Republic of Moldova □ Preparation for clinical trials

19. Date of filling out the communication sheet: ……

20. The doctor who completed communication sheet: NS ..... **Signature:** .....

Practical application 6.4.

Describe 2 case studies regarding the withdrawal of drugs from the pharmaceutical market, according to the model below:

The cause of withdrawal of the drug	Procedure for withdrawal from the pharmaceutical market

Recommended bibliography

1. Bate A., Lindquis M., Edwards I., Olsson S. et al. A Bayesian neural network method for adverse drug reaction signal generation . Eur J of Clin Pharmacol . 2008 , No. 54 , pp. 315-321.
2. Brewer T., Colditz C. Postmarketing Surveillance and Adverse Drug Reactions . Current Perspectives and Future Needs . JAMA. 1999 , no. 281 (9) , pp. 824-829.
3. European Medicines Agency, Guideline on Risk Management System for Medicinal Products for Human Use , London, 14 November 2005, Doc. Ref . EMEA / CHMP / 96268/2005.
4. Jordan S., Knight J., Poiton D. Monitoring adverse drug reactions : scales , profiles , and checklists . You Nurs Rev. 2004 , no. 51, pp. 208-221.
5. Lindquis M. Seeing and Observing in International Pharmacovigilance . Achievements and Prospects in Worldwide Drug Safety . Uppsala (Sweden), Kopierningshuset , 2003.
6. Mann RD Prescription -event monitoring : recent progress and future horizons . Br J Clin. Pharmacol . 1998 , no. 46 , pp. 195-201.
7. Mogoșan C., Farcaș M., Bucșa C. Introduction to pharmacovigilance. Cluj-Napoca, Risoprint publishing house , 2013, 149 p.

Oniga Ovidiu Ionescu Corina - **side effects and drug interactions,** Ed. Medical University "I. Haţieganu ,, Cluj-Napoca, 2004.

CHAPTER 7.

PREVENTION OF ABUSIVE CONSUMPTION OF SUBSTANCES WITH SPECIAL LEGAL REGIME.

Authors: **Corina Scutari, Vladimir Valica, Rodica Peredelcu**

Pharmacist's role in preventing illicit drug use

Drug issues are and will always be one of the dominant themes of socio-political life, not only in the Republic of Moldova, but all over the world, in the difficult attempt to find answers to the many and complex problems related to human existence.

The various sources of information constantly bring to public notice the fact that worldwide, millions of people have fallen prey to the White Death, and the area of drug users is expanding from year to year. According to estimates by the United Nations, INTERPOL and EUROPOL, the drug market ranks second after that of weapons, with profits of billions of dollars annually.

Reality has shown that the scourge of narcotics can be known, combated and controlled, but in no case significantly diminished and even less eradicated. Therefore, it is essential to train specialists in the field of prevention and treatment of the dramatic consequences of illicit drug use, this area of specialization being one of the most difficult and delicate activities within the social assistance, sociology, psychology and medicine.

This reality is increasingly threatening, as in recent years it has become a profitable market for the sale of chemicals, a fact demonstrated by the number of people admitted to health care units or who benefit from social and psychological assistance due to drug use, and by the increasing number of drug-related deaths. The abusive consumption of different chemicals is also widespread for the increase of physical and intellectual performances in the contemporary society. The pharmacist is in direct contact, considering that some of these products are obtained from pharmacies or that some consumers may use the pharmacist to solve certain problems following the abuse.

Objectives

The future pharmacist must know:

- *objectivesThe future pharmacist must know:*
- *chemicals capable of causing drug addicts and their mode of storage and release;*
- *the legal aspects regarding the regime of possession and release of the narcotic, psychotropic and precursor substances;*
- *unwanted effects of drug use and the danger of their occurrence;*
- *the theory and practice of drug counseling depending on the sociology of the victim (the attitude they have to have towards the drug user, differentiated according to the phase in which it is found: drug search or abstinence);*
- *drug addict's therapeutic circuit;*
- *European anti-drug institutions and programs for the authorized support.*

In order to reduce drug trafficking to and from the Republic of Moldova, and to offer and accessibility of all types of drugs, to maintain the tendency to reduce the number of crimes and to increase activism for the purpose of detecting drug traffickers; in reducing and stabilizing the consumption of all types of drugs and the associated consequences that can affect the health of citizens and the development of the society as a whole, a series of **normative acts** have been adopted in recent years:

1. Law no. 1456-XII of 25.05.1993 regarding the pharmaceutical activity.

2. Law no. 1409-XIII of 17.12.97 regarding medicines.

3. Law no. 382-XIV of May 6, 1999 on the circulation of narcotic and psychotropic substances and precursors (Official Gazette of the Republic of Moldova, 1999, no. 73-77, art.339), with subsequent amendments and completions, and fulfilling the commitments undertaken by the Republic Moldova on combating drug addiction and drug abuse.

4. The Criminal Code of the Republic of Moldova no. 985 - XV from 18.04.2002.

5. The State Policy in the field of Medicines, approved by the Decision of the Parliament of the Republic of Moldova no. 1352-XV of 03.10.2002.

6. Order of the Ministry of Health of the Republic of Moldova no. 21 of 12.01.2006 "About approving the criteria for assessing the legal status of medicines regarding their delivery from pharmacies to patients".

7. The Contraventional Code no. 218-XVI of 24.10.2008.

8. Government Decision No. 1208 of 27.12.2010 regarding the approval of the National Drug Strategy for the years 2011-2018.

9. Law No. 185 of 11.07.2012 for the prevention and combating of doping in sports.

The pharmacist, by the nature of his profession, may at any time contact a drug addict who enters the pharmacy to buy a disposable syringe or to try to obtain a specialty based on codeine, benzodiazepines or other medicines that may be used. abusive, either without a prescription or with a counterfeit prescription. The release of these products without a prescription contravenes the law and the Code of Ethics and must be refused, as well as the release on the basis of a counterfeit prescription. Wrong calligraphy of a specialty or a diagnosis not consistent with the usual indications can be indications of falsifying the prescription. On the other hand, the release of an OTC preparation containing codeine to a known heronomaniac who is in abstinence syndrome could alleviate their suffering, but should be accompanied by referral to a detox center.

The offense component provided in art. 2143 of the Criminal Code, excludes synthetic anabolic steroids, testosterone and its derivatives, erythropoietin, growth hormones and chemicals that increase the natural production and release of testosterone or growth hormones from the offense provided in art. 214², because the social danger of these substances is much more serious on human physical and mental health and integrity.

Synthetic anabolic steroids, testosterone and its derivatives, erythropoietin, growth hormones and chemicals that enhance the natural production and release of testosterone or growth hormones are a group of substances of high risk doping substances, particularly dangerous to human life. The need to introduce art. 2144 in the Criminal Code, with the composition of crime for the violation by the responsible persons of the norms regarding the procedure of authorization of medicines, arose as a result of the activity of the commission of investigation, which detected multiple cases of non-observance of the obligatory conditions provided in the law, regarding authorization procedure. The degree of social danger is a very high one, because due to the non-observance of the legal provisions, which provide obligatory steps regarding the analysis of the documentation, but also various laboratory analyzes, some of them are intentionally omitted, medicines are recorded in record time and thus are admitted poor quality drugs on the market, which have no therapeutic effect, but also aggravate the patient's condition. Also, the quality of many drugs on the pharmaceutical market is challenged by both doctors and patients. Many states provide in the Criminal Code a criminal offense for violating the rules regarding the procedure for authorization of drugs.

The pharmacist should not refuse the sale of a single-use syringe, as this may limit the transmission of HIV or hepatitis C, common infections among intravenous drug users. According to a 1987 study in England, it was pointed out that in Edinburgh, where syringes were banned, 51% of drug addicts were HIV positive, while in Glasgow, where free sale was allowed, with educational measures, the percentage of HIV addicts was it was only 5%. Condoms may also reduce the risk of AIDS transmission.

It is important to adopt a syringe replacement program and to distribute anti-AIDS kits (Steribox, a rigid plastic kit containing two disposable syringes, distilled water, alcohol disinfectant pads, a condom and tips to use the components of the kit), in which to be involved, together with non-governmental organizations, the pharmacies.

The pharmacist's dialogue with an addict must be very careful. An unknown drug addict will take advantage of the slightest language error to pressure the pharmacist. At the first contact it must be said as little as possible, and after that visit, it is recommended to say something more. In this way, a favorable time can be reached, when the addict can be given an address and recommendations; intervention is a lasting one. Depending on gender, age, background, medical condition, mental status, present condition and request, the pharmacist's approach may be different, but it must always consider effective communication with the addict.

The role of the pharmacist in the education of the public is also important, as he is the most available health professional and assumes in the next period, with the extension of the drug use, a frequent request by the drug addict. Therefore, he must have a minimum knowledge base in the field of drug addiction, be available for parents who request information and to guide them, when they find in their children regular drug use, especially if it occurs in out of the ordinary entourage, to a doctor competent in the treatment of drug addictions (in drug addiction counseling and detoxification centers, located within the psychiatric clinics).

Drug addicted people should be summited to desintoxication treatment or medical supervision, measures taken in specialized medical institutions, based on forensic expertise. The medical unit may be notified by the

police, by any person who is aware of a drug user, or the drug addict may present at his / her own initiative to a specialized medical unit, and may request confidentiality. The detoxification treatment is performed in the hospitalization regime in one of the medical units established by the Ministry of Health, which are required to periodically check the opportunity to continue the treatment. When no detoxification treatment is required, the person is subjected to medical supervision in a public or private medical unit established by the Ministry of Health, which ensures this activity continuously or temporarily together with a family, person or community that has the necessary skills for a such surveillance.

It is important to use substitution treatment, which involves replacing a high-risk drug, such as heroin, with a substance that induces a lower level of addiction, allowing the treatment of the addict. The intervention is long lasting, the specialists consider, that the duration of the substitution treatment must be almost as long as the duration of the drug use in order to obtain positive results. The substitution represents a series of replacements:

the drug is replaced by a medical product, so an illegal product is replaced by a legal one. This is the most important aspect of the substitution, which allows the addict to be transformed into a "dependent patient under medical treatment and under medical-pharmaceutical supervision." Thus, the physician prescribes the doses and hours of administration, and the pharmacist releases the drug and monitors the absence of treatment or eventual dose increase;

an impure product is replaced by a drug containing a pure substance;

a drug administered parenterally is replaced by a medicinal remedy administered orally or sublingually. Heroine adducted who inject their drug may be a major problem of adaptation to therapy;

the rapid effect is replaced by an effect that is gradually installed; it must be made known to the patient that the rapid effect will no longer be found and that the administration of other substances or medicines to enhance this effect does nothing to compromise the rehabilitation;

multiple doses are replaced by a single dose; only if this mode of administration is followed is it possible, after several weeks, to reduce the dosage very gradually. The dose of the substitution preparation should not produce any euphoria or signs of withdrawal syndrome. The group of friends is replaced by the doctor-pharmacist partnership.

Even if the drug addict, from weakness, consumes heroine, the effect observed will be very weak, because the receptors are blocked by methadone. It is recommended to use methadone in tablets as a substitute. Oral absorption is good, being complete after 2 hours. The effects are observed after 30 minutes, and the maximum effect is observed after 3 hours. The half-life is greater than 24 hours after repeated administration, which explains the possibility of administration in a single daily dose. Methadone is indicated in: severe opioid addiction, characterized by repeated withdrawal failures, despite constant psychological assistance, the existence of a depressive syndrome following a previous intoxication, which only gives up on the administration of opiates and in psychopathological addiction. Methadone is contraindicated in recent drug abuse (less than 2 years), in the absence of motivation to give up; unstable addicts, unable to accept treatment constraints; drug addicts who do not work together to have a positive evolution.

Athletes and medicines

Objectives: The future pharmacist must know the substances that are forbidden to be used by athletes, the pharmaceutical specialties in which they are contained and their mode of delivery, the side effects of long-term use of these substances.

The first definition of doping was given in 1963, which consists of the use of substances or means for artificial growth of the yield, in the perspective or at the occasion of a competition, which can harm the sport's ethics and the physical and mental integrity of the athlete. Doping is forbidden, at international level there is legislation that aims to stop this phenomenon.

At national level, through the Government Decision no. 1208 of 27.10. 2010 Regarding the approval of the National Anti-drug Strategy for the years 2011-2018 and for the purpose of executing Law No. 382-XIV of May 6, 1999 On the circulation of narcotic and psychotropic substances and precursors, with subsequent amendments and completions, and in fulfilling the commitments assumed by The Republic of Moldova on combating drug abuse and drug abuse business has approved the National Drug Strategy for the years 2011-2018, developed in accordance with the European Drug Strategy for 2005, is based on the Single Convention on Narcotics, adopted in New York on March 30, 1961 and amended by the Protocolof modification of the Convention, adopted in Geneva on March 25, 1972, the Convention on Psychotropic Substances, adopted in Vienna on February 21, 1971, the Convention against Illicit Traffic in Narcotic Drugs

and Psychotropic Substances, adopted in Vienna on December 20, 1988, the Political Declaration on to the Principles of the Directors Re drug request, adopted at the Special Session on Drugs of the UN General Assembly in 1988, considered as major legal instruments in addressing drug issues.

The main legislative contributions stipulated in this Government Decision consist of:

- Approval of the National Drug Action Plan for 2011-2013, which is an integral part of the present Strategy.
- Creation of the National Anti-Drug Commission, which presents Anti-drug strategies projects and action plans, coordinates and evaluates their implementation and supervises the fulfillment of the tasks set out in the Strategy and Action Plan.
- The National Monitoring Center for Drugs operates, which prepares the Annual Report on the situation in the field of drugs in the Republic of Moldova.
- There are specialized institutions and organizations involved in reducing drug supply, reducing drug demand and reducing harm.
- The Government of the Republic of Moldova approved the Action Plan on combating drug abuse and drug abuse in 2007-2009.
- In 2007 and 2008, studies were conducted that allowed to obtain a broader picture on drug problems (ESPAD, MARA).
- There are treatment programs, substitution treatment, including in penitentiaries, and harm reduction programs. In some cities, drug action plans have already been adopted locally.
- The Ministry of Internal Affairs is preparing to change the police structure, including the Drug Enforcement Directorate.
- The BUMAD project in Moldova promotes and coordinates drug activities.
- The UNAIDS Office in Moldova supports HIV prevention and harm reduction activities carried out by non-governmental organizations.
- EU-funded twinning projects, to improve data collection systems, as well as to make drug policy more effective at country level.

Also, the Law no.185 of 11.07.2012 was elaborated for the prevention and combating of doping in sport, which implies the prevention and combating at the national level of the phenomenon of doping by adopting and implementing anti-doping policies and regulations; encouraging the practice of a clean sport in order to protect the health of the athletes and to respect the principle of fair play in sports; promoting and supporting research into the phenomenon of doping; promoting the state policy in the field of human health and promoting a healthy way of life. This law refers to:

- Approval of the objectives and purpose, the regulatory domain, the legal framework and the main notions, which include the terms: provisional hearing, doping control (in competition, out of competition, without prior notice), disqualification, falsification, prohibited list, marker, metabolite, officer doping control, assistant athlete personnel, fair-play principle, biological test, positive results, exemption for therapeutic, sports use, including international level, international standard, doping substance, prohibited substance / method, specific substance, suspension, testing doping, treatment, use of prohibited substances or methods.
- Creation of the National Anti-Doping Agency with the approval of the Regulation of organization and functioning, which deals with the prevention and combating at national level of the phenomenon of doping by adopting and implementing the anti-doping policies and regulations; encouraging the practice of a clean sport in order to protect the health of the athletes and to respect the principle of fair play in sports; by promoting and supporting research on the phenomenon of doping in sport.
- Approval of the medical assistance of the athletes with the approval of the therapeutic exemptions, the rules of the medical treatment. The National Anti-Doping Agency ensures the granting of exemptions for therapeutic use for athletes at national level, upon their written request, in accordance with the procedure described in the International Standard for the granting of exemptions for therapeutic use and will report through the Anti-Doping Management and Administration System on the exemptions for therapeutic use granted to athletes of national level who are registered in his registered test batch. The athletes of international level have the obligation to communicate to the National Anti-Doping Agency the requests for granting exemptions for

therapeutic use, submitted according to the provisions of the International Standard for granting exemptions for therapeutic use. Physicians and nurses should pay particular attention to the medical treatment applied to athletes and not recommend, prescribe and administer medicines that contain prohibited substances when they can be replaced with others that do not contain such substances, except exceptional cases; not to recommend, prescribe or cooperate with the use of prohibited methods that are included in the prohibited list; to prevent the use by athletes of prohibited substances and / or methods; to inform the athletes and the national sports federations responsible for the medication administered for therapeutic purposes, its composition and effects on the body; inform the responsible national sports federation as well as the Agency in case a sportsman suspects that they would use prohibited substances or methods to be subjected to targeted testing.

- Approval of the list of prohibited substances. In the fight against doping in sports is also important the integration of the pharmacist, and the ignorance of the susceptible products or their release without medical prescription is an act of professional unconsciousness. Holding a prescription containing medicinal remedies whose active principles are included in the list of doping substances (more often, steroid anabolic agents), the obligatory pharmacist will have to check the validity of the prescription. About falsifying the prescription can indicate the incorrect spelling of the product name or the mismatch between the diagnosis and the accepted indications for the pharmaceutical remedy in question. When receiving a prescription containing drug preparations whose active principles are on the list of doping substances, especially if it is anabolic, the pharmacist should check the validity of the prescription. Wrong name of product or lack of agreement between the diagnosis and the accepted indications for the drug substance in question may indicate that the prescription has been falsified. When releasing the prescription, the pharmacist should inform the patient that the drug is not compatible with participating in sports competitions and warn of the side effects that therapy may have.
- Approval of sanctions in case of doping. Any violation of the anti-doping regulation during the competition automatically attracts the disqualification of the individual results obtained in that competition, with all the consequences resulting from it (withdrawal of the medal, points or prizes), and the use or attempt to use the prohibited substances or methods, as well as their possession is sanctioned with suspension for a period from 2 years to life suspension. In the same way, the refusal or theft from collecting the sample and falsifying the results of the doping control are punished. Illicit marketing of prohibited substances or encouraging the administration of prohibited substances and / or methods are punishable by suspension for a period of at least 4 years, until suspended for life. Persons in the entourage of minor athletes, involved in violating the anti-doping regulations regarding them, are sanctioned with life suspension from sports activity.
- Approval of the list of prohibited substances and methods. The fight against doping is part of the specialty of the pharmacist, and the ignorance of the susceptible products will have doping effects or their release outside the indications. When receiving a prescription containing drug preparations whose active principles are on the list of doping substances, in particular anabolic agents, the pharmacist must check the validity of the prescription. Wrong name of preparation or lack of agreement between the diagnosis and the accepted indications for the drug substance in question may indicate that the prescription has been falsified. When releasing the prescription, the pharmacist must inform the client that the drug is not compatible with participating in sports competitions and warn of the side effects that the therapy may have.

SUBSTANCES AND METHODS FORBIDDEN AT ANY TIME
(both during and outside the competition)

1. ANABOLIZING AGENTS. Anabolic agents are prohibited.

1.1. Androgenic anabolic steroids.

a) Exogenous anabolic steroids: 1-androstendiol; I androstenedione; bolandiol; bolasterone; boldenone; boldion; calusterone; Clostebol; danazol; dehidroclormetiltestosteron; dezoximetiltestosteron; Drostanolone; etilestrenol; fluoxymesterone; formulation, furazabol; gestrinone; 4-hidroxitestosteron; mestanolon; mesterolon; metenolon; metandienonă; metandriol; metasteron; metildienolon; methyl-1-testosterone; metilnortestosteron; methyltrietlolone; methyltestosterone; miboleron; nandrolone; 19 norandrostendionă; norboleton; norclostebol; noretandrolon; oxabolon; oxandrolone; oxymesterone; oxymetholone; prostanozol; quinbolon; stanozolol; stenbolon; 1-testosterone; tetrahidrogestrinonă; Trenbolone and other substances with similar chemical structure or pharmacological effects.

b) Endogenous anabolic steroids: androstendiol; androstenedione; dihydrotestosterone; prasterone; testosterone and the following metabolites and isomers:5α-androstan-3α,17α-diol; 5 α-androstan-3 α,17 β-

diol; 5 α-androstan-3 β,17 α-diol; 5 α-androstan-3 β,17 β-diol; androst-4-en-3 α,17 β-diol; androst-4-en-3 β17 α-diole; androst-5-en-3 α,17 α-diole; androst-5-en-3α,17β-diole; androst-5-en-3 β,17 α-diole; 4-androstendiole; 5-androstendione; epi-dihidrotestosterone; epitestosterone; 3 α-hidroxi-5 α-androstan-I7-one; 3 β -hidroxi-5 α-androstan-17-one; 19-norandrosterone; 19-noretiocolanone.

When a prohibited substance from the above list can also be synthesized naturally in the body, the sample collected from the athlete is considered to contain this prohibited substance when the concentration of the substance, its metabolites, markers or other relevant reports are different. compared to normal human values and cannot be correlated with normal endogenous production. The sample is not considered to contain a prohibited substance when the athlete can provide evidence that the concentration of the prohibited substance, metabolites or markers and / or other relevant reports can be attributed to a pathological or physiological condition. In all cases and in any concentration, the sample is considered to contain the prohibited substance if, on the basis of an accepted analytical method, the laboratory can prove that it is of exogenous origin. In this case no further investigations are required.

In very rare particular cases, in the urine can be found boldene of endogenous origin in very small concentrations, of the order of ng / ml. In these situations, if the laboratory used an accepted analytical method and could not reveal the exogenous origin of the substance, further tests are required. If the athlete does not cooperate during the investigation, the sample is considered to contain prohibited substances.

2.2. Other anabolic agents: clenbuterol, selective androgen receptor modulators, zeranol, tibolone, zilpaterol, and others. These preparations are characteristic of increasing muscle mass and strength and so on. They can cause the following adverse effects: heart and circulatory accidents, kidney and liver accidents, impotence or sterility, growth disorders in young people, serious muscle problems (tendons), etc.

2. PEPTIDIC HORMONES, GROWTH FACTORS AND RELATED SUBSTANCES

✓ Erythropoietin stimulating agents: erythropoietin (EPO), darbepoietin (dEPO), hematide (methoxy polyethylene glycolepoetin beta (CERA)).

✓ Chorionic gonadotrophin (CG) and luteinizing hormone (LH) in men: follitropinum alfa, follitropinum beta, gonadotrophinum chorionicum, goserelin, luteinizing hormone.

✓ Corticotrophins: leuprorelin, tetracosactidum, tryptorelin.

✓ Growth hormone (GH) and growth factors that affect the synthesis / degradation of protein of muscles, tendons or ligaments, vascularization, energy utilization, regeneration capacity or fiber type switching: growth hormone (GH) somatotropin, growth factors of type insulin (IGF-1): somatomedin C, aminotrope-7 anterior pituitary, pituitary growth hormone (pGH), mecasermin; mechanical growth factors (MGFs), derived platelet growth factor (PDGF), fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGF), hepatocyte growth factor (HGF).

✓ Antagonistic hormones and modulators: aromatase inhibitors (aminoglutetimide, anastrozole, androstatriendion, 4-androstern-3,6,17-trione (6-oxo), exemestane, formestane, letrozole, testolactone); selective estrogen receptor modulators (SERMs): raloxifene, tamoxifen, toremifene; other anti-estrogenic substances: clomiphene, cyclophenyl, fulvestrant; agents that alter the function (s) of myostatin: myostatin inhibitors.

The effects sought (are dependent on the substance): increase in strength, increase in the number of red blood cells, better oxygenation, etc. Main side effects: heart and kidney problems, tendon fragility, hypertension and severe vascular thrombosis, hypoglycemia, etc.

3. BETA 2-AGONISTS. All beta-2 agonists, including D- and L- isomers, are prohibited, except that formoterol, salbutamol, salmeterol, and terbutaline may be administered by inhalation for the prevention and / or treatment of asthma and asthma / bronchoconstriction induced by exercise. Medical notification is required, in accordance with the Regulation granting therapeutic exceptions. If salbutamol is found in urine at concentrations greater than 1000 ng / ml, even if a therapeutic exception has been granted, this is considered an adverse analytical result when the athlete cannot prove, by a controlled pharmacokinetic study, that this value is obtained from the use of a therapeutic dose of salbutamol administered by inhalation.

The effects sought: strong anabolic effects in case of systemic administration. Main side effects: heart attacks.

4.DIURETICS AND MASKING AGENTS.

These are products that have the property to modify the excretion of prohibited substances, to mask their

presence in urine or other samples used in doping control, or to modify hematological parameters.

Masking agents include: diuretics, probenecid, plasma substituents (eg albumin, dextran, hydroxyethyl starch and mannitol), and other substances with similar biological effects.

A medical approval in accordance with section 7 of the International Standard for Therapeutic Exceptions is not valid if the athlete's urine sample contains a diuretic in combination with a prohibited substance at or below the threshold.

Diuretics include: acetazolamide, amiloride, bumetanide, canrenone, chlortalidone, ethacrylic acid, furosemide, indapamide, metolazone, spironolaclone, thiazides (eg bendroflumetazide, chlorothiazide, hydrochlorothiazide) and similar to chemotherapeutic or other substances with similar structure or chemotherapy except drosperinone and dorzolamide and topically administered brinzolamide, which are not prohibited).

The sought after effects of diuretics: weight loss (in sports by weight categories: boxing, judo, weightlifting), increasing the volume of urine to favor the elimination of other doping substances, etc. The main side effects of diuretics: brutal hypotension, muscular and cardiac disorders (elimination of a significant amount of mineral salts) etc.

5. PROHIBITED METHODS

Increased oxygen transfer capacity.

Are forbidden:

a) Blood doping, artificial increase of absorption, blood substitutes, micro-encapsulated hemoglobin). It consists of the use of autologous, homologous or heterologous blood or of erythrocyte products of any origin for a purpose other than for legitimate medical treatment.

b) Use of products that increase the capture, transport or release of oxygen, such as perfuoro and efaproxiral derivatives (RSR13), modified hemoglobin-based products (hemoglobin-based blood substitutes, micro-encapsulated hemoglobin products).

PHYSICAL AND CHEMICAL MANIPULATION.

Chemical and physical manipulation: forgery or attempt to falsify, in order to alter the integrity and validity of the samples collected during doping controls (proteases). Alteration or attempt to alter the integrity and validity of the samples collected during the doping control is prohibited.

These include, but are not limited to catheterization, urine substitution and / or falsification. Infusions are forbidden, except in acute medical situations.

GENETIC DOPING

Genetic doping is defined as the non-therapeutic use of cells, genes, genetic elements or modulation of gene expression in order to increase sports performance. Peroxisome proliferator activated receptor 5 agonists (PPAR6) and activated PPAR5-AMP-activated protein kinase (AMPK) agonists are prohibited.

STIMULANTS:

✓ *NONSPECIFIC*: adrafinil, amfeprammon, amifenazole, amphetamine, amphetaminyl, benfluorex, benzfetamine, benzylpiperazine, bromantan, clobenzorex, cocaine, cropropamide, crotetamide, dimethylamphetamine, ethylamfetamine, famprofazine, fenprofilin D-), p-methylamphetamine, methylenedioxyamethamphetamine, methylenedioxymethamphetamine, methylhexanamine (dimethylpentylamine), modafinyl, norfenfluramine, phendimetrazine, fenmetrazine;

✓ *SPECIFIC*: Phentermine, 4-phenylpyracetam (carfedon), prenylamine, prolintan, andrenaline (epinephrine), chain, ephedrine, etamivan, ethilephrine, fenbutrazate, phencamfamine, heptaminol, isomethepten, levmethamphetamine, meclofenoxid, methyphenfine, methylphrine, methylphrine parahydroxyamphetamine, pemoline, pentetrazole, fenprometamine, propylhexedrine, pseudoephedrine, selegiline, sibutramine, strychnine, tuaminoheptane.

All stimulants (including D- and L- optical isomers where applicable) are prohibited except for topical imidazole derivatives and stimulants included in the Monitoring Program 2009. The following substances included in the Monitoring Program 2009 (bupropion, caffeine, phenylephrine) , phenylpropanolamine, pipradol, pseudoephedrine, synephrine) are not considered prohibited substances. Adrenaline associated with local anesthetics or administered locally (eg nasal, ocular) is not prohibited. Catina is forbidden when the concentration in the urine is greater than 5 µg / ml. Both ephedrine and methylphedrine are prohibited when urinary concentrations are greater than 10 µg / ml.

ATTENTION: Ephedrine and its derivatives are frequently used in colds. The effects sought: decrease of fatigue, increase of competitiveness and ageivity, increase of attention, etc. Main side effects: death (amphetamines), hypertension, headache, impaired judgment, etc.

NARCOTICS.

The following substances are prohibited:

- ✓ *Narcotics: buprenorphine, dextromoramide, diamorphine (heroin), fentanyl (remifentanil, sufentanil), hydromorphone, methadone, morphine, oxycodone, oxymorphone, pentazocine, petidine. The effects sought: pain treatment (exceeding the pain threshold). Main effects: respiratory failure, mental and physical dependence, etc.*
- ✓ *Cannabinoids: delta 9-tetrahydrocannabinol (THC) - hashish, marijuana, HU-210 are prohibited.*

GLUCOCORTICOSTEROIDS

All glucocorticoids are prohibited when given orally, rectally, intravenously or intramuscularly. Their use requires obtaining a Therapeutic Exception. Other routes of administration (intra-articular / periarticular / peritendinous / epidural) require medical notification in accordance with section 8 of the International Standard for Therapeutic Exceptions. Topical preparations, when used for dermatological disorders (including ionophoresis / phonophoresis), auricular, nasal, ophthalmic, buccal, gingival and perianal, are not prohibited and do not require the request of medical notification. In some sports, the competition is prohibited some substances such as: alcohol, beta-blockers, diuretics.

There are, according to the World Anti-Doping Agency Code, a number of special substances, which may be the subject of unintentional violations of anti-doping regulations, because they are in the composition of numerous medicinal products or are less likely to be used successfully as doping agents. If the athlete can prove that the use of such a substance was not intended to increase sports performance, the sanction may be reduced.

The pharmacist must know not only the doping substances, but also the products of the composition to which they belong. There are websites on which you can find lists of products that contain such substances and which are constantly updated. It should be noted, however, that some of these products may be subject to therapeutic exceptions.

Practical application 7.1.

Describe 2 cases of steroid anabolics request and pharmacist's recommendations and release tactic to prevent doping.

Requested anabolic	Purpose of administration	Posology	Side effects	Pharmacist's recommendations
1. Metandrostenolone (Danabol, Nerobol)	To improve the use of ingested proteins and increase muscle mass	0.001 g and 0.005 g tablets	Increased AT, atherosclerosis, myocardial ischemia, sudden death, libido changes, impotence, hirsutism, hepatotoxicity, aggression, depression, acne, alopecia, muscle cramps, increased risk of suicide	Only with prescription with the warning of severe adverse reactions by the family doctor
2.				

Practical application 7.2.

Describe 2 cases of psychostimulants request and pharmacist's recommendations and release tactic to prevent doping.

Requested psychostimulant	Purpose of administration	Posology	Side effects	Pharmacist's recommendations
1.				
2.				

Practical application 7.3.

Describe 2 cases of opioid analgesics request and pharmacist's recommendations and release tactic to prevent doping.

Requested opioid analgesic	Purpose of administration	Posology	Side effects	Pharmacist's recommendations
1.				
2.				

Practical application 7.4.

Describe 2 cases of cannabinoids request and pharmacist's recommendations and release tactic to prevent doping.

Requested cannabinoid	Purpose of administration	Posology	Side effects	Pharmacist's recommendations
1.				
2.				

Practical application 7.5.

Describe 2 cases of diuretics / masking agents request and pharmacist's recommendations and release tactic to prevent doping.

Requested diuretic / masking agent	Purpose of administration	Posology	Side effects	Pharmacist's recommendations
1.				
2.				

Practical application 7.6.

Identify, in the pharmacy where you practice, pharmaceutical products containing substances prohibited by the World Anti-Doping Agency.

Product name	Active substance	Pharmaceutical Form / Dose	Producer	Pharmacist's recommendations
1.Testosterone P	Testosterne propionatw	Sol. inj. 1 ml/100 mg/ml	SC Balkan Pharma-ceuticals SRL	Go to doctor. Only with prescription.
2.				

All the products listed above can be considered as xenobiotic. Xenobiotic (from xenos, "foreign") is any chemical compound found in the body but not produced by it. The body acts against xenobiotics by metabolizing them, a process that occurs especially in the liver but also in other tissues. An important consequence of biotransformation is the more or less advanced transition from lipophilia (which favors absorption) to hydrophilicity (favors excretion in urine and faeces), with the exception of volatile compounds which are predominantly eliminated by expiration. The enzymes that participate in the process of metabolizing xenobiotics are called xenobiotic enzymes, they are based in microzomes and are mainly of the type of oxidases, being dependent on NADPH and O2, which is why they are called OFMM "microzomal oxidases with mixed functions". In addition to these oxidases, reductases and hydrolases may also be encountered. The peculiarity of the metabolism of xenobiotics is that the internal "endogenous" enzymes involved in the process cannot distinguish the exogenous substances due to the resemblance to their own substrate.

Biotransformation of xenobiotics into the body takes place under the action of fermentative reactions with metabolite formation.

Practical application 7.7.

Describe 3 cases of biotransformation of pharmaceutical products containing substances prohibited by the World Anti-Doping Agency, indicating fermentation reactions and metabolites formed:

Product name	Oxidation reactions	Hydrolysis reactions	Disalkylation reactions	Hydroxylation reactions	Stomachal absorbtion	Intestinal absorbtion	Metabolits
Codeine			+			+	Morphine
Efedrine		+		+		+	Benzoic acid, norephedrine
Barbiturates		+	+		+		Glucuronide conjugates

Considerations regarding the activity against drug use in the Republic of Moldova

General considerations.

In addressing the problem of drug use, the Republic of Moldova relies on the concept of the World Health Organization "Health for All in the 21st century", according to which drug use is a problem that endangers public health and which could impede the healthy development of citizens and society in a broader context.

Every year, billions of dollars are diverted for antisocial purposes, swelling the pockets of the mafia of drug dealers and gangs of criminals who defy authorities and laws.

Internationally, millions of people fall prey to drugs every year, and a growing proportion of them are completely lost to society.

The recent geo-political conditions in our area have led to an increase in drug trafficking in the territory of our republic destined for the West, which has also favored an increase in the number of citizens who, by means of direct or indirect contact with this phenomenon, have become consumers, dealers, drug dealers.

From examining the causes, conditions and circumstances that have generated, favored or facilitated the trafficking, possession and consumption of drugs, the following can be concluded:

✓ Non-recognition by the vast majority of the population and especially young people, of the legal provisions governing the legal regime of drugs.

✓ Not knowing the consequences to which the drug users are exposed and the consequences of the consumption of drugs or psychotropic substances.

✓ Drug traffickers and dealers generally target young people (students) for drug placement, visiting schools, high schools, colleges, bars, discos, entertainment venues frequented by young people.

✓ The good faith and the precarious economic and financial situation of the inhabitants of the rural area are deceived for the cultivation of plants from the category that can lead to obtaining drugs (Indian hemp, opiates, etc.).

✓ The explotation of the desire of some athletes to achieve great results in domestic and international competitions, which, by implication, can also lead to important rewards.

✓ The existence in the university centers of Chisinau of foreign citizens, students or with other occupations, consumers or drug addicts of all categories, who make every effort to ensure daily doses and implicitly to obtain income from the placement of drugs, to facilitate their work. proper in obtaining drugs.

✓ The state institutions empowered according to the legal regulations with attributions in this field, are insufficiently prepared and superficially equipped logistically to master this problem.

The main reasons for drug use

Curiosity. Most young people are starting to use drugs out of their curiosity to know the effects they have on them or their desire to have new sensations, new experiences.

Showmanship. Drug use can be exciting and challenging. Some people are tempted to face risks without being stopped by warnings as a "danger." You can be looked at positively by others and if you do not use drugs!

Choose from alternatives!

Group pressure. It is very important to know how to say "NO", which shows that you have a strong personality. Try to be yourself even if others think differently.

Problems (in family, at school, with friends). Some young people use drugs to hide or overcome their daily problems (divorce of parents, abuse or indifference of parents or school). We need to understand that drug use can only solve problems seemingly and temporarily. The problems continue to exist and worsen.

Isolation of community or society. Drug use can be a reaction to loneliness, a reaction to problems such as isolation or self-loathing. It is very important to help each other, to solve problems without using drugs. Thus, the problems will be solved in a much more efficient and real way.

How can drug users be recognized?

Early detection of drug users is difficult, especially if the use is occasional. The following indices may suggest possible drug use: sudden behavior change; passing without reason from joy to sadness, sometimes unusual aggression; loss of appetite; gradual loss of interest in school, work, sports, friends; drowsiness and apathy; disappearance of money or valuables; unusual blemishes, strange, chemical odors, on the skin or clothing; the change of the group of friends, the tendency to hide these "friends".

What can we do against drug use?

- ✓ To learn about drugs, to know the truths and myths about them.
- ✓ To provide correct information on the drug problem, to share to others what we know about the causes, consequences and prevention of drug use.
- ✓ To get to know each other better and to have more confidence in ourselves.
- ✓ To develop our critical spirit and adaptive behaviors.
- ✓ To learn how to communicate better with others.
- ✓ Establish a trusting relationship with others.
- ✓ To ask for support and help, when we need it, when we are in difficulty.
- ✓ Let us know who to turn to for qualified help.
- ✓ To guide and help those in need.
- ✓ To take responsibility, to get involved in the prevention of drug use.
- ✓ To undertake educational activities aimed at preventing drug use or delaying the first experience in drug use.
- ✓ **Therapeutic circuit**
- ✓ Definition of terms and expressions according to the Government Decision no. 1208 of 27.12.2010 regarding the approval of the National Anti-drug Strategy for 2011-2018 and Law no. 185 of 11.07.2012 for the prevention and combating of doping in sports:
- ✓ provisional hearing - hearing that takes place immediately after finding a positive result on doping control, carried out by the anti-doping commission of the national sports federation and which precedes the actual hearing;
- ✓ doping control - a process that includes testing planning, collecting and transporting biological samples, laboratory analysis, results management, hearings and calls;
- ✓ competition doping control - doping control in which athletes are selected to be tested in relation to participating in a certain competition;
- ✓ out-of-competition doping control - any doping control that is not performed within the competition;
- ✓ doping control without prior notice - doping control that takes place without any prior warning of the athlete and during which the athlete is accompanied permanently, from the moment of the announcement until the biological sample is taken;
- ✓ disqualification - invalidation of the results of the athlete obtained in a certain competition or sporting events, with all the consequences arising from it, including the withdrawal of medals, points and prizes;
- ✓ counterfeiting - improper action, obstruction, misleading or any fraudulent behavior in order to modify the results of the doping control or to prevent the usual doping control procedures being carried out, as well as to provide false information to the National Anti-Doping Agency;
- ✓ prohibited list - a list that names the prohibited substances and methods;
- ✓ marker - a compound or group of compounds or biological parameters indicating the use of prohibited substances or methods;

✓ metabolite - any substance that appears in the body following a process of metabolization, biotransformation;

✓ doping control officer - a person certified by the World Anti-Doping Agency who has responsibility for the on-site management of the biological sampling session;

✓ assistant athlete personnel - any coach, instructor, manager, sports agent, team leader, official, any medical or paramedical staff and any person who advises the athlete participating or preparing to participate in a sports competition;

✓ fair-play principle - acting in accordance with ethical principles that oppose the concept of success at any price, promoting integrity and equal opportunities for all competitors, emphasizing respect for the personality and value of each participant in a sporting event;

✓ biological sample - any biological material collected for doping control;

✓ positive results - a report issued by an accredited laboratory, which confirms the presence in a biological sample of a prohibited substance, its metabolites or markers or other evidence of the use of prohibited methods;

✓ exemption for therapeutic use - approval of the use for therapeutic purposes of a substance and / or methods prohibited for athletes suffering from a medical condition;

✓ sportsman - a person who systematically or professionally practices a sport discipline;

✓ sportsman of international level - sportsman designated by one or more international sports federations, which is part of the registered test batch of an international federation;

✓ international standard - standard adopted by the World Anti-Doping Agency for the implementation of the provisions of the World Anti-Doping Code;

✓ doping substance - a substance designed to artificially increase human physical capacity or modify the results of sports competitions;

✓ prohibited substance / method - any substance or method so qualified in the prohibited list;

✓ specific substance - any substance so qualified in the prohibited list;

✓ suspension - stopping the athlete or a member of the athlete's assistant staff, for a fixed period of time, from participating in any competition, sports event or sponsorship as a result of the decision taken following the hearing;

✓ provisional suspension - the temporary stopping of the athlete or a member of the athlete's assistant staff suspected of one of the violations of the anti-doping regulations from participating in any competition until the final decision is taken;

✓ doping testing - part of the process of conducting doping control, which involves planning the tests, collecting biological samples, manipulating and transporting biological samples to the laboratory;

✓ Target testing - the selection of athletes for doping tests in which certain specially chosen athletes or groups of athletes are selected based on specific rules for testing at a given time;

✓ therapeutic treatment - treating a health problem with healing or healing agents or methods;

✓ use of prohibited substances or methods - application, ingestion, injection or consumption by any means of any prohibited substance or method.

Therapeutic program - all integrated medical and psychological services and measures, individualized by continuous evaluation, planning, monitoring and adaptation for each dependent consumer, in order to interrupt the consumption, to eliminate the psychological and / or physical dependence and / or to reduce the risks associated with the consumption.

Psychosocial post-treatment-rehabilitation services include the set of measures intended to treat mental dependence and to regain social, professional skills, lost due to drug use.

Measures aimed at reducing the consequences of drug use include outpatient substitution programs and activities to prevent bloodborne illness.

Consumer - the person who is administering or allowing his or her drug to be administered illicitly by swallowing, smoking, injecting, sniffing, inhaling or other means by which the drug can reach the body.

Dependent consumer - the consumer who, following the administration of the drug repeatedly and under necessity or need, presents physical and mental consequences according to medical and social criteria.

Integrated program of assistance to drug users and drug addicts - all health services and psychological and social assistance services provided in an integrated and coordinated manner to drug users, through medical, psychological and social, public, private and mixed units.

Integrated Circuit of Assistance of Drug Addicts and Consumers - All integrated assistance programs provided to consumers and dependents in order to improve the state of health in terms of physical, mental and social well-being of the individual.

Psychological and social program - the totality of individual or group evaluation, counseling and psychotherapy services and of the social services and measures, individualized by continuous evaluation, planning, monitoring and adaptation for each consumer in order to remove his dependence, rehabilitation and social reintegration.

Therapeutic circuit - the set of therapeutic programs applied to the drug addict in a complex, multidisciplinary, multisectoral and continuous way, with the purpose of improving the health status;

Evaluation - determining the psychological and social characteristics of the consumer by the drug prevention, evaluation and counseling centers, in order to include and supervise the consumer in a psychological and social program by the case manager.

Procedures for persons investigated for drug use

If a consumer is sentenced to imprisonment for committing a crime other than those provided for combating trafficking and illicit drug use, the court may order his inclusion in a therapeutic program conducted in the prison system. In the case of committing the named crimes, the prosecutor has, within 24 hours from the beginning of the criminal prosecution, the consumer's assessment by the center for drug prevention, evaluation and counseling, in order to include it in the integrated circuit of assistance of drug users.

After receiving the evaluation report, prepared by the center for drug prevention, evaluation and counseling, based on the forensic expertise within 5 days, the prosecutor has, with the consent of the accused or the accused, its inclusion in the integrated assistance program for drug users .

If the preventive arrest measure has been taken against the accused, it can be revoked or replaced with another preventive measure. In all cases, the criminal prosecution is continued according to the provisions of the Criminal Procedure Code.

If, until the moment the judgment is delivered, the defendant complies with the protocol of the integrated drug assistance program, the court may not impose any sentence on it or delay the application of the sentence.

In case it defers the application of the sentence, the court establishes in the ruling the date on which the sentence is to be pronounced, a time period that can not be more than 2 years, correlated with the duration of the integrated assistance program for drug users.

The time interval between the moment the judgment is pronounced and the date set by the court is a probationary period for the defendant.

For the accused or the defendant who refuses to be included in an integrated assistance program for drug users, the provisions of the Criminal Code and the Criminal Procedure Code apply.

If during the trial period the defendant complied with the integrated drug assistance program, the court may not impose any punishment.

If the defendant does not comply with the integrated drug assistance program, the court may again postpone the application of the punishment, for the same term, and re-inclusion in the integrated drug assistance circuit or apply the penalty provided by law.

The use of drugs under national control, without a prescription, is prohibited in the territory of the Republic of Moldova.

The person who illicitly uses drugs under national control can be included, with his / her consent, in an integrated program to assist drug users. The establishment of the individualized psychological and social program is done by the center for drug prevention, evaluation and counseling, based on the psychological and social evaluation, and in accordance with the results of the medical examination requested by a medical unit.

The establishment of the individualized therapeutic program is made according to the practice protocols, elaborated by the Ministry of Health.

The medical units in which therapeutic programs are carried out for the dependent consumers, transmit to the centers of prevention, evaluation and counseling the drugs necessary to maintain the continuity of the integrated program of assistance of the drug users, based on a medical report.

The therapeutic program and the psychological and social program are carried out in an integrated way, so that the consumer and the dependent consumer can benefit from concomitant and continuous

medical, psychological and social assistance, in compliance with the human rights and the rights of the patient, according to the law.

The psychological and social programs are elaborated by the National Anti-drug Agency in collaboration, as the case may be, with the Ministry of Health, the Ministry of Labor, the Ministry of Justice and can be carried out in centers authorized and / or accredited in this regard, with open or closed regime, public, private or mixed.

The therapeutic programs are elaborated by the Ministry of Health and are carried out in centers established for this purpose, with open or closed regime, public, private or mixed.

The expenses related to the evaluation of the consumer and the development of the psychological and social programs are borne from the state budget through the budget of the National Anti-Drug Agency and, depending on the material possibilities, by the person concerned, family or a private body, under the conditions established by a joint order of the Minister of Administration and Interior, the Minister of Health and the Minister of Finance.

The expenses occasioned by the application of the individualized therapeutic program for the persons insured through the social health insurance system are borne by the health insurance houses of the unique national health insurance fund for the diseases arising from the drug use and through the health programs of the Ministry of Health. and the National Drug Agency's prophylaxis programs.

Depending on the material possibilities, the person concerned, his family or private bodies can partially or completely bear the value of the evaluation services and the expenses occasioned by the participation in psychological and social programs, at the rates and under the conditions established by decision of the president of the National Anti-drug Agency, with the opinion of the ministries concerned.

The amounts collected by the centers for drug prevention, evaluation and counseling represent extra-budgetary revenues of the National Drug Agency, on a permanent basis, and are used to finance programs for the prevention of illicit drug trafficking and consumption. The unused amounts at the end of the year are carried over to the same year for the same year.

The Minister of Justice and the Minister of Health will establish, by common order, the medical and educational measures or programs that will be applied to drug users in penitentiaries.

The personal data of the drug addicts, included in the integrated drug assistance program and of the drug addicts, benefit from confidentiality, according to the norms in force.

The centralized record of the consumers included in the therapeutic circuit is kept by the National Anti-drug Agency, in the unique codified register on drug users, based on the data communicated by the Ministry of Health and other institutions that coordinate therapeutic, psychological and social programs, as well as the established centers, public or private.The Ministry of Health, through the designated directions, has access to the data from the record provided above. All data on persons subject to the integrated drug assistance program and drug addicts will be destroyed 10 years after the cessation of medical supervision. In the case of persons who are repeatedly subjected to integrated consumer assistance programs and drug addicts, the data will be destroyed 10 years after the end of the last period of medical supervision.

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CHAPTER 8.

VEGETAL PRODUCTS, MEDICINAL SPECIES AND PHYTODRUGS.

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Objectives:

- ✓ to know vegetal products, based on active principles in terms of pharmacological action, therapeutic indications, storage conditions.
- ✓ to know the medicinal species and phytomedicines obtained from vegetal products: composition, pharmaceutical forms, pharmacological actions, therapeutic indications, method of administration, storage conditions, precautions and contraindications.

1. Definitions, terminology

Phytotherapy is the treatment, improvment and prophylaxis of diseases and disorders ony kind by means of plants, plant organs or preparations obtained from vegetal products.

Phytotherapy is often associated with *aromatherapy* (treatment of diseases with essential oils, aromatic products and pharmaceutical forms obtained from them), *gemmotherapy* (treatment of diseases with preparations obtained from tree or shrub buds), *apitherapy* (use of honey and honey products) and *homeopathy* (use of tinctures or extracts from plants in very high dilutions). The vegetal product consists of whole medicinal plants or parts of plants (roots, bark, vegetative shoots, aerial parts, leaves, flowers, fruits, seeds, etc.) dried after harvesting, algae, fungi, lichens, presented whole, fragmented or cut, as well as some natural exudates which have not undergone specific processing, used for the preparation of herbal medicinal products in pharmacy or in the pharmaceutical industry.

Vegetal product/ herbal products is represented by whole plant or parts of plants (roots, bark, vegetative shoots, aerial parts, leaves, flowers, fruits, seeds, etc.) dried after harvesting, algae, fungi, lichens, presented whole, fragmented or cut, as well as some natural exudates which have not undergone specific processing, used for the preparation of phytomedicines in pharmacy or in the pharmaceutical industry.

Herbal products must comply with the quality conditions laid down in pharmacopoeias (for officinal products) or other analytical standardisation documentation.

Depending on the intensity of the therapeutic activity of the active ingredients we can distinguish:

- Plants and active substances biosynthesised by the plant cell, *with strong therapeutic action* (plant with alkaloids, cardiotonic heterosides, saponosides), which require adequate dosage and control of administration (*Atropa belladonna, Digitalis sp., Polemonium coeruleum);*
- Plants or vegetal products with a *medium or gentle action* which, when properly administered, produce no side effects (*Crataegus sp., Achillea millefolium, Cynara scolymus* etc.);
- *Plants without toxicity* with polyholozides, vitamins, volatile oils (*Chamomilla recutita, Tilia sp., Rosa canina, Plantago lanceolata, Althaea officinalis*, etc.).

Vegetal products for teas (medicinal species) - one or more vegetal products fragmented or powdered to obtain aqueous extracts by infusion, decoction or maceration, intended for oral use but specific by a unique therapeutic action. Their role is to relax, hydrate, invigorate and relieve the body in certain pathologies, depending on the nature of the active ingredients/principles.

Herbal medicinal product - any medicinal product containing active substances from one or more products of plant origin;

Traditional herbal medicinal product - any herbal medicinal product for which the simplified registration procedure may be applied, if the following conditions are fully met:

(a) the medicinal product, in accordance with its composition, is intended for use without medical intervention for diagnostic purposes, without prescription and/or without monitoring of the medication process;

b) the medicinal product is used in a specific concentration and dose;

c) the medicinal product is intended for oral, topical or inhalation administration;

d) it is documented that the medicinal product has been used in medical practice worldwide - at least 30 years, of which at least 15 years in the European Union and at least 10 years in the Republic of Moldova;

e) there is sufficient data on the traditional use of the medicinal product (safety of use under normal conditions, proven efficacy).

Phytomedicines - medicines containing plant extracts, obtained from vegetal products packaged in modern pharmaceutical forms, with scientifically documented therapeutic effect, used for prevention or treatment, authorised by the Medicines and Medical Devices Agency.

Active principles - chemical compounds synthesised by the plant or animal organism with therapeutic potential.

Active substance (herbal) - any substance or mixture of substances intended for use in the manufacture of a medicinal product and which, through use in the manufacturing process, becomes an active ingredient of the vegetal product, intended to exert a pharmacological, immunological or metabolic action in order to restore, correct or modify physiological functions.

2. Pharmaceutical forms used in phytotherapy

Medicinal plants are used directly by the patient in the form of teas for infusion, decoction, etc., but phytotherapy uses a number of other pharmaceutical forms designed to harness the full therapeutic potential of plants.

Pharmaceutical forms for internal use

✓ **Aqueous extraction solutions:**

- *Infusions* – infusionfor the extraction of active components from vegetal products containing friable tissues (flowers, leaves, aerial parts);
- *Decoctions* - decocting, for the extraction of active components from vegetal products containing woody tissues (roots, rhizomes, bark, fruits);
- *macerates* - maceration, for the extraction of mucilages and thermolabile substances from vegetal products;
- *syrups* - concentrated solutions of sugar in water or other liquids, containing one or more medicinal substances of plant origin.

✓ ***Hydroalcoholic extraction solution:***

- *Tinctures*- obtained by maceration and percolation.

✓ ***Other forms of internal administration:***

- fluid extracts (soft or dried);
- lyophilzed powders-from extractive, aqueous or hydroalcoholic solution;
- capsules, gels, injectable solutions in the composition of which include total extracts or pure activesubstances of plant origin;
- fresh juices from medicinal plants, but especially from fruits and vegetables.

Pharmaceutical forms for external use

- ointments: tinctures, extracts or powders of vegetle products incorporated in the ointment base;
- medicinal oils: obtained by maceration for 4-6 weeks from herball products with vegetaloils;
- inhalations: with essential oil or a mixture of oils or infusions prepared from aromatic plants;
- gargles: by infusion or decoction or from tinctures by dilution with water prepared from vegetal products;
- suppositories – with plant extracts incorporated into the suppository base;
- cataplasms, compresses, patches.

3.Active principles - pharmacological properties

✓ ***Mucilage***

- laxatives, emollients (*Laminariae stipites, Lini semina);*
- expectorants, fluidizers of bronchial secretion (*Althaeae herba, A. radices, Farfarae folia, Malvae flores, M. folia, Plantaginis majoris folia, Tiliae flores cum bracteis, Verbasci flores).*

✓ ***Vitamins***

- surseces de carotins (*Bidenstis herba, Calendulae flores, Hippophaes rhamnoides fructus);*
- rich in vitamin C (*Ribes nigri fructus, Rosae fructus, Sorbi fructus, Viburni fructus);*
- contains vitamin K (*Bursae pastoris herba, Maydis stigmata, Urticae folia, Viburni cortex).*

✓ ***Coumarins and cromons***

- anticoagulant, trombolitic, venotonic (*Meliloti herba);*
- antimicrobian, carminative (*Anethi graveolens fructus, Angelicae rhizomata cum radicibus);*
- fotosensibilizing, toxic (*Ammi majoris fructus, Pastinacae fructus);*
- spasmolytic, coronarodilatator (*Ammi visnagae fructus).*

✓ **Flavonoids**

- sources of rutozide, which increase resistance and decrease the permeability and fragility of blood capillaries (*Fagopyri sagittati herba, Sophorae japonicae alabastra);*
- antiviral (*Scutellariae baicalensis radices);*
- diuretic (*Centaureae cyani flores, Polygoni avicularis herba, Polygoni hydropiperis herba, Polygoni persicariae herba, Ononidis radices);*

- cardiosedative (*Crataegi flores, C. fructus; Leonuri herba);*
- antihypertensive (*Aroniae fructus, Scutellariae baicalensis radices);*
- antioxidant (*Aroniae fructus, Centaureae cyani flores, Crataegi flores);*
- *cholagogue (Helichrysi arenarii flores).*

✓ **Tannins**

- Astringent, antiseptic, precipitates with protein substances (*Alni fructus, Cotini coggygriae folia, Gei rhizomata cum radicibus, Rhus coriariae folia, Pruni padi fructus);*
- haemostatic, antidiarrheal ((*Bistortae rhizomata, Sanguisorbae rhizomata et radices, Bergeniae rhizomata, Hamamelidis cortex, H.folia);*
- healing, in the treatment of wounds ((*Bistortae rhizomata, Quercus cortex);*
- *bacteriostatică (Tormentillae rhizomata, Rhus coriariae folia, Quercus cortex);*
- antidiabetic, antioxidant (*Vaccinii myrtilli cormus, V. m. fructus).*

✓ ***Alkaloids – highly active substances***

- CNS

action - depressant: morphine, codeine (*Papaveris capita),* rezerpina (*Rauwolfiae radices);*

- excitatory: caffeine (*Cacao semina, Coffeae semina, Colae semina, Theae folia*); strychnine (*Strychni semina);* VNS – sympathomimetic: ephedrine (*Ephedrae herba);*
- sympatholytic: ergotamine (*Secale cornutum);*
- parasympathomimetic: pilocarpine (*Sophorae pachycarpae herba);*
- parasympatholytic- atropine (*Belladonnae folia, B. herba, B. radices, Daturae innoxiae herba, D. semina, Hyoscyami folia, Stramonii folia);*
- antispasmodic: papaverine (*Papaveris capita*),
- expectorant: thermopsine (*Thermopsidis lanceolatae herba), glaucine (Glauci flavi herba).*

✓ **Anthracene derivatives** - 1,8-dihydroxyanthraquinone

- laxative and purgative action, depending on the dose (*Frangulae cortex, Rhamni catharticae fructus, Rhei radices, Rumicis radices, Sennae folia, S. fructus*).

✓ **Essential oils**

- antiseptic (*Lavandulae aetheroleum*);
- flavouring, taste corrector (*Citri aetheroleum*);
- stomatic, carminative, antispasmodic (*Coriander aetheroleum, Cumin aetheroleum, Menthae aetheroleum Millefolii aetheroleum, Chamomillae aetheroleum*);
- antibacterial, antifungal (*Thymi aetheroleum, Salviae aetheroleum*);
- expectorant (*Eucalypti aetheroleum, Hyssopi aetheroleum, Thymi aetheroleum);*
  irritants: thymol, thujone (*Absinthii aetheroleum, Juniperi aetheroleum*, Hyssopi aetheroleum, *Millefolii aetheroleum,*
  Tanaceti aetheroleum, Thymi aetheroleum).

Vegetal products used in the preparation of medicinal species

N	Vegetal products(Ph.Eur.; RPh.X, SPh)	Medicinal plant	Active principles	Pharmacologicalaction, uses
1	*Agrimoniae herba,* Ph.Eur.	*Agrimonia eupatoria*	tannins, flavonoids, triterpenes	Astringent – in diarrhea
2	*Alchemillae herba*, Ph.Eur.	*Alchemilla vulgaris*	tannins, flavonoids	Astringent, anti-inflammatory – in diarrhea
3	*Althaeae folia,A. radices,* RPh X, Ph.Eur.	*Althaea officinalis*	mucilages	Emollient – macerated or infused. External: yawning. Internal: in inflammation of the airway and gastrointestinal tract
4	*Anserinae herba,* Ph.Eur.	*Potentilla anserina*	tannins	Astringent, hemostatic, antidiarrheal, antiseptic. Externally: inflammation of the oralcavities, bleeding. Internal:diarrhea

5	*Betulae folia,* *B. gemmae,* Ph.Eur	*Betula pendula* fla	vonoids	Diuretic – in bacterial and bacterial conditions inflammatory of the urinary tract
6	*Bursae pastoris herbaa,* Ph.Eur.	*Capsella bursa-pastoris*	flavonoids, vitamins	Hemostiptic – in menorrhagia
7	*Calendulae flores,* RPh X, Ph.Eur.	*Calendula officinalis*	saponins, flavonoids,volatile oil	Anti-inflammatory, *antispasmodic* – in gastritis, gastrointestinal spasms; inflammation of the skin and the mucous membranes.
8	*Cardui benedicti* *Herba, SPh*	*Cnicus benedictus*	bitter substances, flavonoids	Bitter tonic, stomachic
9	*Silybi marianifructus,* PhEur, *SPh*	*Silybum marianum*	silymarin - mixture of flavonolignans (silybin, sili cristina, silidianina), flavonoids	Hepatoprotector, hepato regenerator – in prophylaxis and the treatment of hepatic diseases
10	*Centaurii herba,* Ph.Eur.	*Centaurium umbellatum,* *C. erythrea*	*secoiridoid* glycosides (*ge ntiopicrina*)- the *bitter* tasting	Bitter – in dyspeptic states, tostimulate appetite
11	*Chelidonii herba,* RPh X, Ph.Eur.	*Chelidonium majus*	isochinolinic alkaloids	Cholagogue, antispasmodic – inbiliary diseases. Fresh latex – for destroying warts
12 *fl*	*Crataegi folia,ores, fructus,* RPh X, Ph.Eur	*Crataegus monogyna, C. laevigata*	proanthocyanidins, flavonoids	Coronary expansion, positive inotropic, antiarrhythmic; sedative
13	*Cynarae folia* RPh X, Ph.Eur	*Cynara scolymus*	depside (cinarine and other derivatives of chlorogenic acid), flavonoids, sescviterpeniclactones	Infusion: cholesterol, cholecystokinetic Standardizedextract: hepatoprotective, hepatoregenerative, Hypolipidemi, chypocholesterolemic
14	*Echinaceae herba,* *E. radices*, Ph.Eur	*Echinacea purpurea,* *E. pallida,* *E. angustifolia*	polysaccharides, derivatives of caffeic acid	Immunostimulant – in the preventionand treatment of infections of the upper respiratory tract, genitourinary system and skin
15	*Equiseti herba* RPh X, Ph.Eur	*Equisetum arvense*	saponins, flavonoids, saltsof potasium	Diuretic increases the level ofdiuresis without altering the electrolyte balance – in cysts, urethritis, urinary lithiasis,rheumatism
16	*Farfarae folia,* Ph.Eur	*Tussilago farfara*	mucilage, small amounts of pyrrolizidine alkaloids	Emollient inflammations – in the mouth and respiratory tract
17	*Filipendulae ulmariae herba,* Ph.Eur	*Filipendula ulmaria*	phenolic compounds, flavonoids, tannins	Antipyretic, anti-inflammatory,diuretic
18	*Frangulae cortex* RPh X, Ph.Eur	*Rhamnus frangula*	anthracene glycosides	Laxative, purgative
19	*Fraxini folia,* Ph.Eur	*Fraxinus excelsior*	chlorogenic acid derivatives, flavonoids, tannins, secoiridoids	Diuretic, laxative – inrheumatism, gout
20	*Fumariae herba,* Ph.Eur	*Fumaria officinalis*	isochinolinic alkaloids	Dilation of the gallbladder – in hypercholesterolemia increasedbiliary secretion – in hyperkeratosis bile secretion decreases
21	*Gei rhizomata,SPh*	*Geum urbanum*	tannins	Antidiarrheal, astringent,antiseptic
22	*Gentianae radices,* RPh X, Ph.Eur	*Gentiana lutea*	*bitter* principles *(gentiopicroside)*	Bitter tonic

23	*Graminis rhizomata,* Ph.Eur	*Agropyron repens*	polysaccharides	Diuretic, purifying
24	*Hyperici herba* RPh X, Ph.Eur	*Hypericum perforatum*	naftodiantrone, flavonoids	Antidepressant, choleretic
25	*Leonuri cardiacae herba,* Ph.Eur	*Leonurus cardiaca*	flavonoids and terpenoids	Sedative, hypotensive, positiveinotropic, chronotropically negative –in cardiac neurosis.
26	*Lini semina*, FRX, Ph.Eur	*Linum usitatissimum*	mucilage	*Emollient laxative*, emollient in gastritis, *enteritis*
27	*Liquiritiae radices,* RPh X, Ph.Eur	*Glycyrrhiza glabra*	*triterpene saponins* (*glycyrrhizin)*, flavonoids	Expectorant, secretolythic,spasmolytic – pharyngitis, laryngitis
28	*Lupuli strobuli,* Ph.Eur	*Humulus lupulus*	oleoresin with bitter floroglucins *(humulone, lupulone)*	Sedative, bitter tonic
29	*Lichen islandicus*, Ph.Eur	*Cetraria islandica*	bitter substances, mucilage	Bitter tonic, antiseptic, emollient – in dry cough, bronchitis.
30	*Malvae flores, M. folia,* Ph.Eur	Malva sylvestris	mucilage	Emollient – in coughing,laryngitis
31	*Marrubii herba,* Ph.Eur	*Marrubium vulgare*	bitter substances	Bitter tonic
32	*Maydis stigmata,* RPh X	*Zea mays*	flavonoids, salts of potasium	Diuretic
33	*Myrtilli fructus siccus,* Ph. Eur	*Vaccinium myrtillus*	tannins, antocianine	Anti-diarrhoeal
34	*Ononidis radices*, Ph.Eur	*Ononis spinosa*	saponins, flavonoids	Diuretic
35	*Passiflorae herba,* Ph. Eur	*Passiflora incarnata*	alcaloids, flavonoids, phloroglucinol derivatives	Antispasmodic, sedative
36	*Plantaginis folia (Plantaginis lanceolate* folia), Ph.Eur	*Plantago sp.* mu	cilage, iridoids(*aucubin*)	Emollient, anti-inflammatory inrespiratory diseases
37	*Plantaginis ovatae semina and Pl.ov.seminis tegumentum* , Ph.Eur	*Plantago ovata*	mucilage	Laxative
38	*Primulae radices*, RPh X,Ph.Eur	*Primula veris, P. elatior*	saponins	Expectorant – in respiratorydiseases
39	*Psyllii semina,* Ph.Eur	*Plantago afra, P. arenaria*	mucilage	Laxative
40	*Quercus cortex,* Ph.Eur	*Quercus roburr Quercus petraea*	tannins	Anti-diarrhoeal
41	*Rhei radices*, Ph.Eur	*Rheum palmatum, Rheum officinale*	anthracene glycosides, tannins	Laxative – in large doses (1-3g). Astringent -– in small doses (0.1-0.5 g)
42	*Rosae fructus,* Ph.Eur	*Rosa canina*	vitamin C, carotenoids	Vitaminising
43	*Salicis cortex,* Ph.Eur	*Salix species*	salicylic alcohol derivatives	Anti-inflammatory, antirheumatic
44	*Sambuci flores*, Ph.Eur	*Sambucus nigra*	flavonoids, *phenols, carboxylic acids*	Diaphoretic – in the fever flu
45	*Sennae folia S.fructus*, Ph.Eur	*Cassia angustifolia, C.acutifolia*	anthracene derivatives La(sinosides)	xative – in acute constipation

46	*Symphyti radices*	*Symphytum officinale*	allantoin, saponozides, mucilage, pyrolyzidine alkaloids	Anti-inflammatory, healing -external
47	*Solidaginis herba,* Ph.Eur	*Solidago canadensis, S. gigantea*	flavonoids, saponins	Diuretic
48	*Solidaginis virgaureae herba*, Ph.Eur	*Solidago virgaurea*	flavonoids, sapononis	Diuretic
49	*Taraxaci radices*, *T. herba* Ph.Eur	*Taraxacum officinale*	bitter substances	Stomachic, choleretic, depurative
50	*Tiliae flores* RPh X, Ph.Eur	*Tiliae species*	mucilage, volatile oil	Diaphoretic in fever, sedative
51	*Tormentillae rhizomata,* Ph.Eur	*Potentilla erecta*	tannins	Astringent, anti-diarrhoeal
52	*Urticae folia, U. radices,* Ph.Eur	*Urtica dioica*	sterol compounds, lectins	Leaves: diuretic Roots: in urinary disorders due tobenign prostatic hyperplasia
53	*Uvae ursi folia,* Ph.Eur	*Arctostaphylos uva-ursi*	*phenolic glycosides* (*arbutoside*)	Urinary antiseptic
54	*Valerianae radices,* Ph Eur	*Valeriana officinalis*	iridoids, valepotriatesvolatile oil	Sedative
55	*Verbasci flores*, Ph.Eur	*Verbascum phlomoides, V. thapsiforme*	mucilage, flavonoids,iridoids, saponins	In respiratory diseases, cough
56	*Violae tricoloris herba,* Ph.Eur	*Viola tricolor*	flavonoids, *salicylic acid derivative*, saponins	Diuretic, expectorant
57	*Vitis-idaeae folia, SPh*	*Vaccinium vitis idaea*,	*fhenolic glycosides* (*arbutoside*)	Urinary antiseptic

Vegetal products with strong action that are included in standardized phytopreparations and vegetal products with active principles that are not extracted into water

N	Vegetal products (Ph.Eur.;FRX)	Producing species, popular name	Active principles	Pharmacological action, uses
1	*Aconiti tuber,* RPh X	*Aconitum napellus* (Aconite)	terpenic alkaloids(*aconitine*)	External: local anesthetic Internal: antinevralgic – in trigeminal neuralgia, chronic joint inflammation; centralantitussive
2	*Adonidis herba,* SPh	*Adonis vernalis* (Spring pheasant's eye)	cardiotonic heterosides (*adonitoxin*)	Internal: cardiotonic (diuretic, sedative)
3	*Agni casti fructus,* Ph.Eur.	*Vitex agnus castus* (Chaste tree)	iridoids, flavonoids, labdan type diterpene	Premenstrual syndrome and menstrual cycle anomalies
4	*Allii sativi bulbus,* Ph.Eur.	*Allium sativum* (Garlic)	sulfur compounds (*allicin,* respectively sulfoxides)	Antibacterial, antimycotic hypotensive, hypocholesterolemic
5	*Aloe cormus, A. folia,* RPh X, Ph.Eur	. Aloe *species (Aloe)*	anthraquinone glycosides	Laxative, purgative – in constipation
6	*Belladonnae folia*, RPh X, Ph.Eur.	*Atropa belladonna* (Belladonna)	tropane alkaloids	Antispastic, antisecretory, midriatic
7	*Cimicifugae rhizomata*	*Cimicifuga racemosa* (Black bugbane)	triterpenes type cycloartenol glycosides (actein)	Menopausal and post-menopausal disorders

8	*Colchici semina, C. bulbus* Ph.Eur.	*Colchicum autumnale* (Autumn crocus)	alkaloids (colchicine, demecolchicine)	Demecolchicine – in myeloid leukemias, colchicine – in gout
9	*Convallariae herba,* Ph.Eur.	*Convallaria majalis* (Lily-of-the-valley)	cardiotonic heterosides	Cardiotonic and coronarodilatator agent – heart failure
10	*Cucurbitae semina* Ph.Eur,	*Cucurbita pepo* (Pumpkin)	tocopherols, selenium, sterols	Benign prostatic hyperplasia, urinary disorders
11	*Digitalis purpureae folia,* RPh X, Ph.Eur.	*Digitalis purpurea* (Foxglove)	cardiotonic heterosides	Inotrop positive, chronotrop negative – heart failure
12	*Eleutherococci radices,* Ph.Eur.	*Eleutherococcus senticosus,* (Siberianginseng)	eleutherosides (oleanolicacid derivatives), polyholosides	Immunostimulant, adaptogen – in states of fatigue, overwork, convalescence
13	*Ginkgo folia,* Ph.Eur.	*Ginkgo biloba* (Ginkgo)	terpenic derivatives (bilobalide, ginkgolides), flavonoids	Special extract EGb 761: anti-ischemic, anti-edema, anti- hypoxic, anti-radical action, improves the rheologicalproperties of blood
14	*Ginseng radices,* Ph.Eur.	*Panax ginseng,* (Ginseng)	saponosides (ginsenosides)	Adaptogen, geriatric remedies
15	*Hederea folia,* Ph.Eur.	*Hedera helix* (The common ivy)	triterpenic saponosides	Expectorant, antibacterial,antifungal – in whooping cough, bronchitis, asthma; dermal disorders, cellulite
16	*Hellebori rhizome,* PhEur	*Helleborus niger, H. purpurascens,* (Helleborus specoes)	cardiotonic heterosides of bufadienolid type, saponosides	Anti-inflammatory, antirheumatic
17	*Hippocastani semina,* Ph.Eur., SPh	*Aesculus hippocastanum,* (Horse-chestnut)	saponosides (*escin*)	Anti-inflammatory, anti-edematous anti-exudative – in varicose veins, thrombophlebitis, leg ulcer etc.
18	*Hyperici herba,* RPh X, Ph.Eur.	*Hypericum perforatum* St John's wort	Anthracene derivatives (*hypericin, hyperforin*)	Standardized hypericin extract: antidepressant Oily macerate: healing, anti-inflammatory
19	*Orthosiphonis folia,* Ph.Eur.	*Orthosiphon aristatus* Java Tea	flavonoids, K salts, caffei cacid	Diuretic, smooth muscle spasmolytic – in urinary tract infections, kidney stones
20	*Rusci aculeati rhizome,* Ph.Eur.	*Ruscus aculeatus* Butcher's broom	saponosides (*ruscogenol*)	Vasoprotective, venotonic, anti-inflammatory – in varicose veins and hemorrhoids

Medicinal plants - sources of essential oils

N.	Medicinal plant / Family/ Popular name	Volatile oil	Pharmacological action, uses
1	*Lavandula officinalis,* Lamiaceae (Lavender)	*Lavandulae aetheroleum*	Antimicrobial, sedative, flavoring, anti-viperin
2	*Coriandrum sativum,* Apiaceae (Coriander)	*Coriandri aetheroleum*	Tonic, antimicrobial, stomachic, antiparasitic,flavoring
3	*Mellissa officinalis,* Lamiaceae (Lemonbalm)	*Mellissae aetheroleum*	CNS sedative, anti-inflammatory, choleretic,healing, flavoring
4	*Citrus aurantium, Rutaceae*	*Aurantii aetheroleum*	Flavoring, taste corrector, insecticide

	(Bitter orange)		
5	*Citrus aurantium ssp. Bergamia,* Rutaceae (Bergamot orange)	*Bergamotae aetheroleum*	Tonic, antibacterial, antispastic, antiseptic, anti-inflammatory
6	*Citrus limon,* Rutaceae (Lemon)	*Citri aetheroleum*	Flavoring, taste corrector
7	*Mentha piperita,* Lamiaceae (Peppermint)	*Menthae aetheroleum*	Digestive stimulant, anti-infectious, antispastic, analgesic, anesthetic (local), antidiarrheal, anti-inflammatory, taste and odor corrector
8	*Mentha crispa,* Lamiaceae (Curly mint)	*Menthae crispae aetheroleum*	The same actions as peppermint oil
9	*Carum carvi,* Apiaceae (Caraway)	*Carvi aetheroleum*	Stomachic, carminative, spasmolytic, cholagogue-choleretic, galactagogue, flavoring
10	*Anethum graveolens,* Apiaceae (Dil)l	*Anethi aetheroleum*	Stomachic, carminative, spasmolytic, diuretic, condiment
11	*Eucalyptus globulus,* Myrtaceae (Blue gum)	*Eucalypti aetheroleum*	Secretolytic, expectorant, respiratory and renal antimicrobial, vermifugal, antirheumatic
12	*Rosmarinus officinalis,* Lamiaceae (Rosemary)	*Rosmarini aetheroleum*	General tonic, cardiotonic, antispastic, stimulantof blood circulation, expectorant, antimycotic, antibacterial, diuretic, mucolytic, flavoring,condiment
13	*Thymus vulgaris,* Lamiaceae (Common thyme)	*Thymi aetheroleum*	Antimicrobial, antiparasitic, general tonic, antispastic, flavoring, condiment
14	*Thymus serpyllum,* Lamiaceae (Wild thyme)	*Serpylli aetheroleum*	General tonic, neurotonic, stomachic,antimicrobial, antiparasitic, analgesic
15	*Satureja hortensis,* Lamiaceae (Summer savory)	*Saturejae aetheroleum*	General tonic, neurotonic, antimicrobial, antiparasitic, analgesic, immunostimulant, flavoring, condiment
16	*Origanum vulgare,* Lamiaceae (Oregano)	*Origani aetheroleum*	Antimicrobial, antiparasitic, general tonic, immunostimulant
17	*Arnica montana,* Asteraceae /(Mountain arnica)	*Arnicae aetheroleum*	Anti-inflammatory, antimicrobial, healing,anthelmintic, oxytocic, analgesic
18	*Salvia officinalis,* Lamiaceae (Garden sage)	*Salviae aetheroleum*	Antispastic, mucolytic, antibacterial, cholagogue-choleretic, antiviral, antifungal,antihemorrhagic, estrogen, emenagogue, healing (toxic!)
19	*Pinus silvestris,* Pinaceae (Scots pine)	*Pini aetheroleum*	Anti-bronchitis, anti-asthmatic, antiseptic,flavoring
20	*Juniperus communis,* Cupressaceae (Common juniper)	*Juniperi aetheroleum*	Tonic-stomachic, antiseptic, anti-inflammatory, analgesic, revulsive
21	*Chamomilla recutita,* Asteraceae (Chamomile)	*Chamomillaeaetheroleum*	Anti-inflammatory, antispastic, anti-ulcerous,carminative, healing, epithelizing, antifungal
22	*Achillea millefolium,* Asteraceae (Common yarrow)	*Millefolii aetheroleum*	Anti-inflammatory, healing, anti-hemorrhagic,cholagogue-choleretic, antifungal
23	*Artemisia absinthium,* Asteraceae (Wormwood)	*Absinthii aetheroleum*	Tonic bitter, stomachic, vermifug, emenagogue(toxic!)
24	*Zingiber officinale,* Zingiberaceae (Ginger)	*Zingiberis aetheroleum*	Anti-anorexigenic, carminative, choleretic, antiulcerous, anti-inflammatory, antiplatelet, antiemetic
25	*Inula helenium,* Asteraceae (Elecampane)	*Inulae aetheroleum*	Antibacterial, antifungal, anthelmintic, antispastic, choleretic, diuretic, antifermentative
26	*Cinnamomum sp.,* Lauraceae (Camphor tree)	*Cinnamomi aetheroleum*	Antimicrobial, antiparasitic, respiratory and circulatory stimulant, carminative, stomachic, antiseptic

27	*Eugenia caryophyllata,* Myrtaceae (Clove tree)	*Caryophylli aetheroleum*	Antimicrobial, antiparasitic, general stimulant,anti-inflammatory, analgesic
28	*Anisum vulgare*, Apiaceae (Pimpinella)	*Anisi aetheroleum*	Antispastic, expectorant, antiseptic, bactericidal, vermifug, stomachic, carminative, galactagogue, estrogen, emenagogue, flavoring
29	*Foeniculum vulgare,* Apiaceae (Common fennel)	*Foeniculi aetheroleum*	Antiseptic, bactericidal, carminative, stomachic, galactagogue, antispastic, analgesic, estrogen
30	*Ocimum basilicum,* Lamiaceae (Basil)	*Basilici aetheroleum*	Antibacterial, spasmolytic, carminative, stomachic, eupeptic, flavoring, condiment
31	*Acorus calamus,* Acoraceae (Calamus)	*Calami aetheroleum*	Flavoring, insecticide

Medicinal plants contraindicated in pregnancy

The use of medicinal plants during pregnancy is a common phenomenon. Many women have used one or more plants during pregnancy. Some women used herbal products in the first trimester, while others used them throughout their pregnancy. Various studies have shown that the use of plants in the first 12 weeks and the last 12 weeks of pregnancy is dangerous for the foetus. Pregnant women should consult the doctor or pharmacist before using any plants or vegetal products.

N	Medicinal plant	Arguments for contraindications
1	*Achillea millefolium* (Yarrow)	Bitter substances, essential oil,(emenagogic - *thujone)*
2	*Acorus calamus* (Calamus)	Essential oil, bitter substances, (stimulates uterine contractions)
3	*Artemisia sp.* (Wormwood)	Bitter substances, essential oil, (stimulates uterine contractions- *thujone*)
4	*Berbersi vulgaris (Barberry)*	Isoquinoline alkaloids – *berberine, oxiacantine* (stimulates uterine contractions)
5	*Capsicum annuum* (Pepper)	Acyclic alkaloids – *capsaicine* (stimulates uterine contractions)
6	*Chelidonium majus* (Celandine)	Isoquinoline alkaloids – *chelidonine, chelerythrine* (emenagogic action)
7	*Dryopteris filix-mas* (Male ferm)	Phloroglucine –*filixic acid* (stimulates uterine contractions)
8	*Ephedra distachya* (Ephedra)	Acyclic alkaloids – *L ephedrine, pseudoephedrine* (stimulates uterine contractions)
9	*Foeniculum vulgare* (Fennel)	Essential oil (stimulates uterine contractions)
10	*Glycyrrhiza glabra* (Liquorice)	Saponins – *glycyrrhizinic acid* (stimulates uterine contractions)
11	*Juniperus communis* (Common juniper)	Essential oil, bitter substances (emenagogic action)
12	*Lavandula officinalis* (Lavander)	Essential oil (emenagogic action)
13	*Linum usitatissimum* (Flax)	Poliholosides (emenagogic action)
14	*Passiflora incarnata* (Passiflora)	Indole alkaloids– *harman, harmin, harmol* (stimulates uterine contractions)
15	*Phytolaca americana (American* pokeweed)	Saponins, *phytolaccosides* (stimulates uterine contractions)
16	*Podophyllum peltatum* (Mayapple)	Lignans – *podophylline* (emenagogue, stimulates uterine contractions
17	*Rhamnus frangula* (Buckthorn)	Anthracene derivatives– *frangularozide* (emenagogue, abortive action)
18	*Salvia officinalis* (Garden sage)	Essential oil, estrogen substances ((stimulates uterine contractions)
19	*Tanacetum vulgare* (Tansy)	Essential oil– *thujone* (stimulates uterine contractions)
20	*Thymus vulgare* (Ggarden thyme)	Essential oil– *thujone* (stimulates uterine contractions)

21	*Viscum album* (Mistletoe)	Polypetide fractions – *viscotoxin* (stimulates uterine contractions)

4. Release of vegetal product, medicinal species and phytomedicines

The release of medicinal products from plants involves several aspects: single vegetal products and mixtures of vegetal products (medicinal species) containing two or more products with established therapeutic activity, which determine the organoleptic characteristics (appearance, taste, smell) of the other species. Medicinal species must not contain toxic products. Phytomedicines may be included in the OTC (over-the-counter) or Rx (prescription) list, which the student has learned during the undergraduate course. The secondary packaging indicates the components (vegetal products) of the products.

When releasing these products during the undergraduate internship, the student will pay particular attention to the following aspects:

- ✓ whether the patient is self-medicating,
- ✓ will ensure that the requested product has the indication for the declared condition (beware of popular names),
- ✓ will provide the necessary information on how to administer it,
- ✓ contraindications, side effects, drug interactions,
- ✓ preparation method (vegetal products, medicinal species),
- ✓ the patient is advised to contact their doctor and/or pharmacist if their health does not improve.

VEGETAL PRODUCTS, MEDICINAL SPECIES AND PHYTOMEDICINES

Warning the patient to consult the doctor if the health condition does not improve in short time.

Practical application 8.1.

Describe 5 vegetal products*:*

1. The name of vegetal product, pharmaceutical form, dose, packaging, manufacturer;
2. Latine name of vegetal product, plant species and family;
3. Chemical composition of vegetal product;
4. Pharmacological action and usage;
5. Mode of preparation and administration;
6. Precautions and contraindications.

	1.	2.	3.	4.
Od. Nr.	**The name of vegetal product, pharmaceutical form, packaging, dose, manufacturer**	**Latine name of vegetal product, plant species and family**	**Chemical composition and active principles**	**Pharmacological action and usage**
	Frunze de pătlagină (Broadleaf plantain), 50g N1, Manufacturer: Medfarma, Republic of Moldova	***Plantaginis majoris folia*** 50g *(Plantago major,* Fam. Plantaginaceae)	***Plantaginis majoris folia*** *(Broad leaf plantain contain mucilages: xylose 40%, aucubin, allantoin, flavonoids, tannins, vitamins: A, K, C)*	*Emollient (mucilages), haemostatic (vitamine K), astringent action (tannins), in inflammatory conditions and hypoacid gastritis, in the treatment of coughs of various aetiologies, chronic bronchitis, bronchial asthma, gastroduodenal ulcer.*
5.	**Mode of preparation and administration.** Internal use: infusion of 1 teaspoon of vegetal product with 200 ml boiling water; infuse for 5-7 minutes; filter and take 3 times a day			
6.	**Precautions and contraindications.** Until the present, have been not reported adverse effects or toxic phenomen. Contraindications - hypersensitivity to the substances in the product composition.			

Practical application 8.2.

Describe 5 medicinal species *(consisting of several vegetal products)*

1. The name of medicinal species, pharmaceutical form, dose, packaging, manufacturer;

2. The constituents of medicinal species and indication of latine name of vegetal products, plant species, family;

3. Chemical composition and active principles;

4. Pharmacological action and usage;

5. Mode of preparation and administration;

6. Precautions and contraindications.

Od. Nr.	1. The name of medicinal species, pharmaceutical form, dose, packaging, manufacturer	2. The constituents of medicinal species and indication of latine name of vegetal products, plant species, family	3. Chemical composition and active principles	4. Pharmacologic action and usa
	Specie coleretică N1 (***Cooleretic species N1),*** Fragmented vegetal produc, 50g, N1, Manufacturer: Medfarma, Republic of Moldova	*Tanaceti flores 10g, Calendulae flores 15g, Menthae piperitae herba 10g, Chamomillae flores 15g, Coriandri fructus 25g, Achileae millefolii herba 25g*	***Tanaceti flores*** (2% bicyclic monoterpenoids: thujone (toxic) and tanacetone); ***Calendulae flores*** (3% carotens); ***Menthae piperitae herba*** (monoterpenoids:menthol, menthon); ***Chamomillae flores*** (1,9% sesquiterpenoids: chamazulene, matricine, matricarine); ***Coriandri fructus*** (1,4% acyclic monoterpenoids: *linalool, geraniol);* ***Achileae millefolii herba*** (bitter substances: artabsine, absinthine and anabsinthine)	Choleretic. cholag in biliary dyskinesia gastrointestinal spasms, acute and chronic hepatitis, cholecystitis
5.	**Mode of preparation and administration.** Internal use: infusion of 1 teaspoon of medicinal species with 200 ml boiling water; infuse for 15 minutes; filter and take after a meal, 2-3 times a day.			
6.	**Precautions and contraindications.** Contraindications - hypersensitivity to the substances in the compos of the product, precautions by thjone (*Tanaceti flores*)			

Practical application 8.3.

Describe 5 phytomedicines (multicomponent)

1. The name of phytomedicines, pharmaceutical form, dose, packaging, manufacturer;
2. The constituents of phytomedicines;
3. Chemical composition and active principles;
4. Pharmacological action and usage;
5. Mode of preparation and administration;
6. Precautions and contraindications.

Od. Nr.	1. The name of phytomedicines, pharmaceutical form, dose, packaging, manufacturer	2. The constituents of phytomedicines	3. Chemical composition and active principles	4. Pharmacological action and usage
	Bronhostop syrup, syrup,120 ml, N1, Manufacturer: Pharma GmbH, Austria	*Extractum Althaeae radices fluidum 55,3 mg, Extractum Thymi vulgaris siccum 8 mg*	***Extractum Althaeae radices fluidum*** *(Althaeae radices -30%* polyholosides wich by hydrolysis give galactoze, ramnoze, arabinoze, galacturonic acide, starch); ***Extractum Thymi vulgaris siccum*** *(Thymi vulgaris herba-1,2%* aromatic terpenoids: thymol)	Expectorant, antitussive, anti-inflammatory, secretolytic, promotes expectoration of mucus, viscous in cough associated with cold
5.	**Mode of preparation and administration.** Bronchostop syrup is taken orally for 5 days. It can be take undiluted or diluted in water or warm tea, in the dose mentioned in the leaflet, depending on age.			
6.	**Precautions and contraindications.** Not recommended for children under 12 years of age. Hypersensitivity reactions, gastrointestinal disorders have been observed for *Extractum Thymi vulgaris*.			

* ***8.1, 8.2*** *and* ***8.3*** *to be completed with vegetal products, medicinal species and phytomedicines, authorised as medicinal products****, do not include food supplements;***

** *of the 15 products described,* ***at least 3 must be manufactured in the Republic of Moldova****.*

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Chapter 9.

BIOLOGICAL MEDICINES. FOOD SUPPLEMENTS AND SPECIFIC FOOD. NUTRITION ELEMENTS.

Author: **Livia Uncu**

BIOLOGICAL MEDICINES

Enzyme medicines.

Systemic enzymes play as true therapeutic agents, stimulating the innate therapeutic potential of the body. They recover the used cells, removing the useless material, eliminating unhealthy cholesterol from the blood; produce hormones; maintain homeostasis and nourish the neurotransmitters responsible for memory and our affective states.

Due to certain *recovering and rejuvenating* properties of the body metabolic enzymes are indispensable, in particular for the older adults. Because the normal physiological process leads to the degradation of organs and systems (and finally to death) with age, therefore the human body is no longer able to produce the same number of enzymes as in youth. When the body is no longer able to produce enzymes of a fixed type, it suffers from fatigue, indigestion, nausea, irregular stools, flatulence, sinusitis, obesity, autoimmune and metabolic disorders. It is very important to note that in the lack of the enzyme (due to a poor dietary food) nutrients, such as vitamins and minerals, are not absorbed by the body. They are activated only in combination with enzymes. If this combination does not occur, all this will be eliminated by urine.

Vaccines

Imunoterapia is aimed to use all pharmaceutical forms that transfer antibodies or induce antibody formation in the body. It takes two forms:

- ✓ *passive immunotherapy*-intake of antibodies in the form of IG immunoglobulins;
- ✓ *active immunotherapy* – induces the formation of antibodies.

Active immunotherapy is also called vaccinotherapy (active immunoprophylaxis) and consists of the administration of the vaccine (an antigen) to the host to induce formation of antibodies and cell-mediated immunity:

- ✓ It is practiced to induce protection against many infectious agents and may utilize either inactivated (killed) materials or live attenuated agents, lacking toxicity and virulence, therefore cannot cause disease in healthy people, but can elicit protective immune response similar to that produced by natural infection;
- ✓ Active immunization requires time (about 1-2 weeks, sometimes about 1-2 months) to develop and is therefore generally inactive at the time of a specific exposure.

The vaccine is an immunological medicine containing a suspension of whole-cell pathogen (live or inactivated) or its fractions (specific pieces) takes to induce immunity and elicit a strong protective immune response for the purpose of preventing diseases or their consequences.

The requirements for vaccines:

- ✓ to induce and maintain significant levels of specific antibodies and / or specific cellular immunity;
- ✓ to create a strong and long-lasting immune response after a single administration;
- ✓ to be well tolerated and have minimal side effects;
- ✓ to be suitability for mass immunization
- ✓ to be stable under various conditions (temperature, light, transportation).

Nowadays, immunization is the best method to limit the distribution of fatal illnesses. The systematic immunization of the population leads to the significant reduction of the morbidity, resulting in infectious diseases, due to vaccination, mortality and invalidity, that has been called by these diseases. All this leads to the significant reduction of the social and economic damage caused by these diseases as well.

Nowadays, the Program for the years 2016-2020 is approved by the Government of the Republic of Moldova. The aim of this Program is to eliminate or reduce morbidity, invalidity and mortality by providing the population with mandatory immunizations, guaranteed by the state, against tuberculosis, viral hepatitis B, polio, diphtheria, tetanus, whooping cough, measles, mumps, rubella, *Haemophilus influenzae* type B, with rotavirus, with pneumococci, as well as by way of additional immunizations from epidemic indications of contingents with high risk for disease, spread of infection and death. This way we can protect little babies, the elder, pregnant women or just people with a weak immune system

In order to achieve the objectives of this Program, the following vaccination calendar is applied:

Recommended immunization schedule in the Republic of Moldova.

Vaccination	**Immunization** against								
	Hepatitis B (HBV)	Tuberculosis	Poliovirus (OPV)	Infectiei Hib	Diphtheria, tetanus and pertussis	Tetanus-diphtheria	Measles-mumps-rubella	Rotavirus	Pneumococcal infections
	HepB	BCG	OPV	Hib	DTP	DT/Td	MMR	RV	PCV
24 hours	HepB-0								
2-5 days		BCG-1							
2 months	HepB-1		OPV-1	Hib-1	DTP-1			RV-1	PCV-1
4 months	HepB-2		OPV-2	Hib-2	DTP-2			RV-2	PCV-2
6 months	HepB-3		OPV-3	Hib-3	DTP-3				
12 months							MMR -1		PCV-3
22-24 months			OPV-4		DTP-4				
6-7 years		BCG-2	OPV-5			DT	MMR -2		
15-16 years						DT	MMR -3		
Adults aged 20, 30, 40, 50 and 60 years						DT			

Source: Government Decision of RM "regarding the approval of the National Immunization Program for the years 2016-2020" N1113 of October 6, 2016.

Practical application 9.1

*Complete the table with the characterization of **2 biological medicinal products** of different classes (enzymes, vaccines, immunoglobulins, hormones) according to the examples in the Practice Guide*

	Trade name, composition, pharmaceutical form	**Quality control peculiarities**	**Special features of storage, validity (including after opening the package)**	**Peculiarities of administration**	**Comments, recommendations**
Medicines from extracts of animal origin (enzymes)					
Digestive enzymes	Triferment, dragees: Dragees contain trypsin 18 U.I., lipase 6 U.I. and amylase (amylolytic power) 6.5 g	Physico-chemical methods; Determination of enzymatic activity.	Keep in a dry and cool place, out of the sight and reach of children; Validity 3 years	Adults and children aged over 3-4 years, 1-2 dragees a day	During or immediately after eating a meal and drink plenty of water

	Trade name, composition, pharmaceutical form	Quality control peculiarities	Special features of storage, validity (including after opening the package)	Peculiarities of administration	Comments, recommendations
Vaccines					
Whole – Agent, Subunit vaccine	**Tuberculosis vaccine** (BCG), lyophilized powder and solvent	Immunochemical methods; microbiological control; sterility, pyrogenicity	Keep at temperatures 2-8 degrees, in a dry place, out of the sight. Validity 2 years. Prescription medicine. Don't store more than 24 hours at 2-8 degrees after opening the package.	According to the vaccination schedule.	Don't freeze!
Immunoglobulins					
Monoclonal or polyclonal antibodies	**Normal human immunoglobulin**; immunologically active protein fraction from human serum or plasma, contains 10% albumin	Physico-chemical methods; Immunoturbidimetric method	Keep at temperatures 2-10 degrees, in a dry place, out of the sight. Validity 2 years. Prescription medicine.	Adults and children aged over 10 years 3 ml	It is administered only i.m., absolutely contraindicated i.v.
Hormonal medicines					
Insulin	**Humulin Regular,** rapid-acting solution for injection, 100 U/ml -3 ml in cartridges.	Physico-chemical methods; Biological dosing; Determination of bacterial endotoxins; Zn content; related proteins;	Keep at temperatures 2-8 degrees, in a dry place, out of the sight. Class B. Validity 2 years. Prescription medicine.	It is water soluble, it is administered s.c., in exceptional cases - i.m.	Don't freeze!
Medicines used in hemorrhagic diseases					
Heparin	**Lioton 1000 Gel,** Heparin 100000 U, Gel; 50 g in tubes	RMN, electrophoresis, determination of bacterial endotoxins; pyrogenicity, residual solvents; biological dosing.	Keep at cool place. Table B. OTC. Validity 3 years.	It is applied to the skin in the injured place by light friction 1-3 times a day	Don't massage.

Specific nutrition

Healthy nutrition is vitally important for the body throughout life to orchestrate a range of physiological functions to maintain health. Some nutrients we need in relatively large quantities - macronutrients such as proteins, carbohydrates, lipids (fats), etc., others in relatively small quantities - micronutrients: vitamins, mineral salts.

Nutrition is the study of nutrients in food and focused on the biochemical steps (how the body breaks food down and repairs and creates cells and tissue) through which substances inside us are transformed from one form to another to provide the important nutrients our body needs for growth and development.

A nutrient is a component of consumed food required by organisms and cells to stay alive

Nutrition During Pregnancy, Lactation

Recommendation on nutrition, supplying the caloric intake, should not be made mechanically, it should be individualized according to the age of the pregnant woman, occupation, lifestyle, especially woman's pre-pregnancy weight (women who are overweight or have obesity have lower caloric intake for recommended total gestational weight gain compared to normal-weight or under-weight women).

Nutrients required during pregnancy: Recommended protein intake is about 36 g/ day, carbohydrates is 5-6 g / kg body / day; fats - 1 g / kg body / a day; fruits and vegetables (apricots; mango; peaches; papaya; kale; pumpkin; beet; raw broccoli or gulley; carrots; cabbage; salad; spinach), fiber (cereals, fruits and vegetables), iron (an additional daily intake - about 800 -1000 mg Fe), *folic acid; vitamins (Vit. B6, Vit. B12, Vit. A, Vit. C, Vit. D), water and fluids (6 to 8 cups a day)*. *By and large, in the case of a normal pregnancy nutrition should follow the following principles:* the pregnant woman can eat what she wants in convenient quantities; food should be salted to taste without excess; use only iodized salt; avoid foods preserved by salt; foods should be in a balance between animal products (meat, eggs, milk and milk preparations) and vegetable products (especially various fruits and vegetables); second half of pregnancy should be administered daily as a prevention 30-60 mg elemental Fe and folic acid.

Breastfeeding women should consume a well-balanced diet providing adequate intakes.
Breastfeeding women should consume a balanced
diet providing adequate nutrient intakes

Recommendation on nutrition of breastfeeding women: milk 500-600 ml or yogurt 250-300 ml; cow cheese (are good dietary sources of calcium, protein and vitamin D, that is used to build a baby's bones and teeth); 5-6 eggs per week; many vegetables and fruits, without abuse; all vegetables and fruits are recommended; onions, garlic, cabbage, cauliflower can change the flavor of the breast milk, besides they should not be excluded unless the child refuses breast (this has exposed your baby to different tastes since intrauterine life and which might help child more easily accept solid foods down the road); meat, chicken, beef, sometimes pork; fats: oil (especially in salads!), cream, butter; water (still!), herbal teas (decaffeinated teas), fruit juice (watch out for added sugar), in total at least between1 and 2 liters (from all sources) a day.; the diet shouldn't be high in salt and use only sea salt, because it contains a very important element – iodine.

Nutrition for children:

Recommendation on nutrition of children: It is recommended a diet rich in**: Ca** (toddler, 1-to 3- year-old children, need about 500 milligrams of calcium a day; preschool, 4- to 8-year-old children - 800 milligrams a day; grade-schoolers, 9- to 13-year-old children need 1300 milligrams a day); **Fe** (2-to 8- year-old children need 10 mg of Iron a day: girls aged 11 - 14 years need 15 mg; boys at the same age need 12 mg a day); **Zn** (2-to 8- year-old children need 10 mg of Zinc a day: girls aged 9 -14 years need 12 mg; boys at the same age need 15 mg a day); **Vitamin D** (2-to 13- year-old children need 200 IU (International Units), that is the biological equivalent of 5 mg a day); Vitamin A (1-to 3- year-old children need 400 mcg of vitamin A a day ; at 4-6 years of age - 500 mcg a day; at 7 - 10 years of age - 700 mcg a day. Girls aged 9 -14 years need 800 mcg a day; boys at the same age need 1000 mcg a day); Vitamin C (1-to 3- year-old children need 15 mg of vitamin C a day; at 4 - 8 years of age - 25 mg a day; at 9-13 years of age- 45 mg a day); liquids (with low level of added sugar), does not require to drink tea instead of water, even it is very hot. Daily guidelines of water for 2-year-old children is 115 - 125 ml / kg / day; for 4-year-old children is 100-110 ml / kg / day; for 6 –year- old children is 90-100 ml / kg / day;

To limit your child's calories from: foods rich in sugar and saturated and trans-fats such as *biscuits, cakes, sweet drinks, chocolate, sweets, chips and pastries.*

Nutrition for teens

Recommendation on nutrition of teens: to avoid diets and starvation; to choose the different nutrients (grains, meat (including fish) and eggs, dairy products, fruits and vegetables); to limit unhealthy nutrients such as added sugar (sweets and sweetened fruit juices), salt and saturated and trans fats; to increase intake of complex carbohydrates (good sources include whole-grain bread, potatoes, rice, flour and cereals are sources of complex carbohydrates); adequate protein intake of animal origin, which provide the highest quality proteins teens need (animal sources include meat, fish, eggs, dairy) and adequate protein intake of plant origin (peas, beans, soy, nuts); calcium intake; iron intake (iron sources can be natural (meat, fish, green leafy vegetables, peas, beans) or from supplement intake); phosphorus and iodine intake (fish, seafood, dairy products, dried beans and pasta); scheduling meals.

Nutrition for young and older adults

Recommendation on nutrition of young adults: to eat 5-9 fruits and vegetables a day; to keep a right balanced intake of essential fatty acids by avoiding saturated fat-rich foods; to include foods rich in vegetable and fruits; to limit the intake of refined carbohydrates; to follow the regimen to drink a large quantities of liquids (minimum 2 liters per day); daily supplementation with vitamins and minerals in case of an inadequate diet.

Recommendation on nutrition of older adults: they must monitor their dietary decisions and make sure their caloric intake provides the energy that they require, without going into excess, should eat fewer energy-dense carbohydrates, especially refined, sugar-dense sources, particularly for those who lead a more sedentary lifestyle; proteins (1g/kg); they should choose unsaturated fats over saturated fats (extra virgin olive oil); minerals (primarily calcium and iron); vitamins (vitamin D, which help prevent some diseases, such as osteoporosis, vitamin C, necessary to maintain arterial integrity, repair tissues and strengthen the capillaries, group B vitamins, which facilitates all food assimilation processes, serves to produce red blood cells and stimulates brain activity.)

Practical application 9.2

*Complete the table with the characterization of **3 dietary supplements** for pregnant women, infants, preschoolers, young and older adults, that have been found in the pharmacy, according to the examples in the Practice Guide*

Product name	Composition, active substances	Pharmacological effect	Indications for use	Specific recommendations
AZINC Menopause	Zinc, Calcium, Vitamin E, Vitamin D3, Beta Carotene, Omega 3 and Omega 6.	The beta-carotene in the composition of the product takes care of the skin, eyes and helps us to obtain a healthy tan, which will last much longer. The product also contains vitamin E as an antioxidant, which keeps the body young. It can also get rid of the waves of excessive perspiration, maintain optimal calcium in the body and prevent the installation of osteoporosis. It's a good soothing and helps the skin not to lose its firmness.	Azinc Menopause is intended exclusively for women and can be administered at the first signs of menopause. Azinc Menopause offers solutions for biological disorders of women in middle age. Due to menopause, metabolism slows, leading to osteoporosis and aging of the skin. Addition of calcium, phosphorus and vitamin D are essential in the fight against menopausal symptoms.	This nutritional supplement should be administered at the first signs of menopause, for 3 months, followed by a one-month break. One capsule / day after lunch, with a large amount of water.

NUTRITION THERAPY RECOMMENDATIONS IN VARIOUS PATHOLOGIES

Nutrition in diabetes

Foods allowed without weighing: vegetables (nettle, turnips, spinach, pumpkin, radishes, cucumbers, green peppers, cauliflower, artichokes, eggplants, tomatoes, gooseberries, celery, salad, cabbage, mushrooms, green beans, raw pumpkin).

Foods allowed only with weighing: bread, flour, cereal products, dried legumes, potatoes, rice, dairy,

fruits (melons, strawberries, strawberries, avocados, melons, grapefruit, lemons, cherries, tangerines, apricots, peaches, kiwi, pineapple, raspberries, oranges, blackberries, blueberries, quince, cherries, black currants, nectarines, plums, apples, pears, pomegranates, bananas); seeds (dried walnuts, sunflower seeds, peanuts, dried pumpkin seeds); vegetables (onion, donut, carrot, parsley, red beet, green peas, garlic, dried lentils).

Forbidden foods: sugar and sugary products, sweets, chocolate, syrups, pastries and confectionery, jams, sweets, dried plums, figs, raisins, soft drinks, honey, brown sugar, ice cream.

Nutrition in atherosclerosis (ATS)

Recommended: organically grown fruits and vegetables (especially grapefruit, grapes); soy beans and other soy products; garlic and onion; tomatoes and tomato-based products; extra virgin olive oil; fish meat: salmon, tuna, herring, mackerel, halibut; whole-grains; oats, due to the high fiber content; oilseeds, especially nuts and almonds; peanuts; sesame seeds, sunflower and pumpkin; blueberries red; teas; tomato juice; grape juice.

Forbidden foods*:* foods high in cholesterol and saturated fat.

Nutrition in heart failure and hypertension

Allowed foods: low-fat milk, unsalted cheese, lean meat, preferably fish, poultry or beef in the amount of 150-200 g / day 2-3 times a week, prepared by boiling, grilling or baking; 2-3 eggs per week, only in food preparations; occasional butter; daily vegetable oils, added raw in the food, in quantity depending on the caloric requirement; 1 a day old unsalted bread according to the caloric requirement; boiled vegetables and fruits (compotes, sausages, mashed potatoes, soups, puddings), or raw; the flavored spices instead of salt (parsley, dill, tarragon, thyme); to made food more acidic use only lemon; homemade sweets, avoiding the baking soda and salt, preferably dry dough or biscuit dough, fruit gelatin, pelts; allowed drinks: herbal tea, fruit and vegetable juice, milkshakes, skim milk, yogurt, barley coffee; sparkling drinks are contraindicated.

Forbidden foods*:* saturated fats; sugar; caffeine and nicotine; alcohol; excess of sodium, calcium magnesium and vitamin C.

Nutrition in asthma

Allowed foods: organically grown fruits and vegetables; fish meat: salmon, mackerel, herring and halibut; extra virgin olive oil; flax seed; rosemary, ginger, turmeric.

Forbidden foods*:* milk and other dairy products, which aggravate asthma symptoms; other vegetable oils; margarine; very salted foods; preservatives and dyes, such as MSG (monosodium glutamate), tartrazine sulphates (E102).

Nutrition in postoperative states

Postoperatively nutrition rules that patients must do:

- ✓ To eat varied food at the regular intervals.
- ✓ There is no need to change your nutrition, but just how to cook food.
- ✓ Chew well and swallow slowly.
- ✓ After the operation, the stomach can't hold more than 100 g. You will feel full after only a few spoons of food.
- ✓ Do not over eat!
- ✓ It is better to avoid foods that cause bloating of the freshly operated patient: crudities, potatoes, olives, borsch
- ✓ Fruits and vegetables can be eaten in the first weeks in the form of compote, baked in the oven or on the grill.

Practical application 9.3

*Complete the table with the explanation of 3 special nutrition regimens, that have been found in the pharmacy, **for any 2 pathologies**, according to the examples in The Practice Guide:*

Pathological process	Recommended foods	Forbidden foods	Specifications for age, gender	Recommendations
Diabetes	Tomatoes, peppers, mushrooms, cucumbers, cabbage, eggplant, leeks, salad, carrots, celery, beets, dried onions, garlic; melons, lemons, strawberries, cherries, currants, nuts; meat, fish	sugar and sugary products, sweets, chocolate, syrups, jams, dried plums, figs, raisins, cold sweet drinks, honey, brown sugar, ice cream.	carbohydrate intake for older children, derived by fruits, vegetables	frequent meals (7 times a day), checking the level of sugar in monkeys

	and their derivatives; milk and derivatives (cheeses, cream, wheat, butter); eggs; non-alcoholic beverages prepared without sugar (with sweeteners).		and whole grains.	

FOOD SUPPLEMENTS

Food supplements are as an addition to a normal diet, which are concentrated sources of nutrients (i.e. mineral and vitamins) or other substances with a nutritional or physiological effect that are marketed in "dose" form (e.g. pills, tablets, capsules, liquids in measured doses). Food supplements are intended to correct nutritional deficiencies, maintain an adequate intake of certain nutrients, or to support specific physiological functions. They are not medicinal products and as such cannot exert a pharmacological, immunological or metabolic action. Therefore, their use is not intended to treat or prevent diseases in humans or to modify physiological functions. Nowadays, there are the following normative acts regarding food supplements in the Republic of Moldova:

- ✓ LAW Nr. 78 / 18.03.2004 on food products. Published: 28.05.2004 in The Official Monitor Nr. 83-83 art Nr: 431 Implemented: 28.05.2005
- ✓ LAW Nr. 10/ 03.02.2009 on the state supervision of public health Chapter IV, THE SANITARY AUTHORIZATION OF PRODUCTS, SERVICES AND ACTIVITIES, Art. 24.
- ✓ LAW Nr. 318 /27.12.2012 for changing and supplementing certain legislative acts. Published: 08.03.2013 in The Official Monitor Nr. 49-55, art Nr: 152, Art. X. – Law nr. 10-XVI in 3 February 2009
- ✓ LAW Nr. 93 / 26.04.2012 on the modification and completion of some legislative acts. Published: 20.07.2012 in The Official Monitor Nr. 149-154, art Nr: 482, Implemented: 20.09.2012
- ✓ LAW Nr. 50 / 28.03.2013 on official controls to verify the law accordance with legislation regarding the animal feed and food products and with health regulations and animal wellbeing. Published: 07.06.2013 in The Official Monitor Nr. 122-124, art Nr: 383
- ✓ LAW Nr. 113 / 18.05.2012, on the establishment of general principles and requirements of food safety legislation. Published: 13.07.2012 in The Official Monitor Nr. 143-148 art Nr: 467 Implemented: 13.01.2013
- ✓ Informative note to the Government decision "Regarding the notification of food supplements" (http://old.ms.md). Nowadays, the requirements regarding placing food supplements on the market are partially regulated by Government Decision no. 538 of September 2, 2009 for the approval of the Health Regulation regarding food supplements.

According to LAW No.78 of 18.03.2004 nutrients and / or food supplements are considered as nutrients, such as proteins, lipids, carbohydrates, vitamins, mineral elements, essential amino acids, and / or preparations produced in tablets, capsules, dragees, powders or liquids, which are composed of macro- and micronutrients and / or other edible substances and are consumed in defined quantities, in addition to the usual food ration. Nutrition and / or dietary supplements are not medicines;

A functional nutrient is one that provides the meet certain nutritional essential substances to the body (vitamins, carbohydrates, lipids or proteins) that ensures beneficial physiological effects on some chronic diseases.

Natural health product is an intermediate term between nutrient and medicine, which is treated or crude products, intended for human consumption to maintain and improve your health.

Nutrients are the substances that may be a food or part of an element, which provide a medical or health benefit, including the treatment and prevention of diseases.

The main classes of nutraceutical products are: phytoestrogens, phytosterols, carotenoids, plant fibers, polyunsaturated fatty acids, phenols, probiotics and prebiotics, other food antioxidants (Coenzyme Q10).

Phytoestrogens (isoflavones) are plant-derived compounds, appear in food in the form of **water-soluble glycosides** (dadzein, genistein, and glycitein). Effects on the human or animal organism: anti-aging, hypolipedemia, antisclerotic, anticancer, estrogenic, anitestrogenic, anti-inflammatory. They are mainly found in soy beans and food by-products prepared from these beans (milk, tofu).

Phytosterols are a group of plant-derived compounds (are found in corn oil extracts, rape, sesame, soy) that are structurally similar to cholesterol in the human body. When consumed, they compete with

cholesterol absorption in the digestive tract, blocking it and, as a result, lowering blood cholesterol levels. Phytosterols are added to functional foods of athletes to recover efforts and prevent cell damage especially in a marathon race The secretion of cortisol, as a stress hormone with a catabolizing function, can be controlled, and its concentration can thus be reduced, which is a benefit in terms of protecting the muscle mass.

Carotenoids - Alpha and beta-carotene are found in carrots, fruits and vegetables. They play a important role in the body, which is to neutralize free radicals with high reductive potential. Lutein is found in fresh green vegetables. Its role in the body is to reduce the risk of getting senile macular degeneration (reducing the sensitivity of the retinal yellow spot to light sensors). It acts and prevents opacification of the cornea in the incipient cataract. **Lycopene** is found in tomatoes and the products / in food products extracted from these plants. It has an effect on pre-tumor and tumor disorders, reducing the risk of these disorders, which was proved by the mega- studies, which have been applied on animals and humans. It significantly reduces the risk of developing aggressive prostate cancer for men.

Practical application 9.4

Complete the table with characterization of dietary supplements containing isoflavones, carotenoids and phytosterols, that have been found in the pharmacy, according to the examples in the Practice Guide: ***1 example of product for each nutraceutical.***

Product name	Composition Content of active ingredients (isoflavones, carotenoids and phytosterols)	Sources of obtaining	Pharmacological effect	Indications for use	Specific recommendations
Fito 40 with soy isoflavone	flax seed oil, alpha-tocopherol acetate (vitamin E), soy isoflavones, beeswax, coconut oil, palm oil, calcium ascorbate (vitamin C), calcium carbonate, magnesium carbonate, folic acid, starch of rice	**Soy**	Isoflavones ensure phytoestrogenic effect. In medicine, soy isoflavones are used as a hypotensive remedy, which strengthens the nervous and cardiovascular systems, diminishes the heat blows during the menopause. Soy isoflavones normalize the hormonal background and thus control the processes that trigger the uncontrolled growth of cells (hyperplastic processes) in the human body, which prevents the formation of malignancies.	FITO-40 ensures the female body with substances needed for certain periods of life, eliminating the following signs: headaches, blisters, insomnia, overwork, restlessness, hair problems, decreased libido, increased triglyceride and cholesterol levels, weight gain, formation adipose tissue etc. It is used to prevent the formation of the osteoporosis, the development of breast and prostate cancer.	adults and children over 12 years of age - 1 capsule 3 times a day during eating a meal and drink plenty of water, for 1-3 months

Vegetable fibers are the insoluble fibers (cellulose and hemicellulose), represented by the products of the milling and bakery industry such as wheat bran, corn, rice, having an effect on reducing the tumor risk in colon cancer and breast cancer for women. Soluble fibers and beta-glucans, represented by the fibers, which are found in barley, oats, flaxseed, ensure an effect on reducing cardiovascular disease, heart disease and certain cancers. It also has the potential to reduce blood lipids (LDL- low density lipids) and total cholesterol. It should be mentioned that a high fiber diet requires to consume more liquids.

Polyunsaturated fatty acids (Vitamin F) - Polyunsaturated fatty acids (often abbreviated to PUFA) can be subdivided into two groups depending on their chemical structure: n-3 and n-6. Omega-6 family (linoleic acid, arachidonic acid, docosapentaenoic acid); omega-3 family (α-linolenic acid, eicosapenthaenoic acid, docosahexaenoic acid). **Linoleic acid** is the main representative of category n-6. This category is mainly found in vegetable oils. **Alpha linolenic acid** is the precursor of group n-3. As sources we can specify certain

vegetable oils (soy, rapeseed, flax). There is evidence that high consumption of alpha linoleic acid favors lead to reducing of morbidity and mortality. **Eicosapentaenoic acid (EPA)** and **docosahexaenoic acid (DHA)** are two important representatives of the n-3 group. They are found especially in fatty fish and in omega-3 rich vegetable oils (rapeseed and soybean). EPA and DHA have a strong effect of lowering blood triglycerides while their action on cholesterol is less important. They also have beneficial effects on blood pressure, coagulation and heart rate.

Phenols -anthocyanins represent a group of highly active phytochemicals, which are found in fruits. They play an important role of neutralizing the free radicals and reducing the risk of different types of cancer. Catechins, flavonoids and flavones are found in citrus fruits, vegetables, fruits and tea. They provide neutralization of reactive oxygen and free radicals, reduction the risk of aggressive cancer. The lignans are found in different vegetables, rye and flax. They prevent colon cancer and carry out the normal function of the excretory apparatus. Tannins, known as primary forms from which anthocyanins derive, are mainly found in cocoa, chocolate products, cherries, blackberries, black currants. Reduce the risk of cardiovascular disease and optimize the activity of the urinary tract.

Prebiotics are nongistible substances that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth or activity of advantageous bacteria that colonize the large bowel by acting as substrate for them. The most common prebiotics are: oligofructose (fructooligosaharides - FOS), lactulose, inulin, galacto-oligosaccharides. **Fructo-oligosaccharides (FOS),** which are found in artichokes, onion powder, bananas, soybeans, beans, are non-digestible and resistant to breakdown by stomach acid and enzymes in the human gastrointestinal tract. They have the capacity to optimize the quality of the flora of the terminal intestine and to contribute to the normal health of the digestive system.

Probiotics are live microorganisms that are intended to have health benefits when consumed or applied in adequate quantities to the body. Probiotics influence the intestinal ecosystem by stimulating the mucosal immune and non-immune system mechanisms by competing with potential pathogens; The benefits of probiotics have been tested in various measures for a number of diseases: intestinal infections, cancer, diarrhea (pediatric, tourist, associated with antibiotics), inflammatory bowel disease and irritated bowel syndrome, constipation. Probiotics may contain a variety of microorganisms. The most common are bacteria that belong to groups called *Lactobacillus* and *Bifidobacterium*. Other bacteria may also be used as probiotics, and so may yeasts such as *Saccharomyces boulardii*.

Coenzyme Q10 is most commonly used for conditions that affect the heart such as heart failure and fluid build up in the body (congestive heart failure or CHF), chest pain (angina), and high blood pressure. It is also used for preventing migraine headache, Parkinson disease, and many other conditions, but also for strengthening the immune system and restoring energy and speeding recovery after physical exertion. It can be given in combination with other drugs (e.g. beta-blockers) to counteract the unwanted effects on the functioning of the heart, muscles or other organs.

Melatonin ensures property of strengthening the the immune system, has strong antioxidant effects and is responsible for regulating sleep.

Octacosanol (polycosanol) is a natural supplement obtained from sugar cane, where the main ingredient is octacosanol. Octacosanol is an alcohol, which is found in the wax film, which cover some leaves and fruits. Citrus leaves and bark contain octacosanol, as well as wheat germ oil. The caviar contains large quantities of octacosanol.

Picnogenol is the most potent antioxidant at the moment and acts as a protector against environmental toxins.

Lutein is an important antioxidant that can be a solution for myopia, improving blood circulation to the eyes.

Astaxanthin: possesses a marked antioxidant activity; moreover, a recent study confirmed its anti- inflammatory efficacy: its administration reduces the expression of inflammation-related molecules (IL-6, ICAM, VEGF).

Alpha-lipoic acid is an antioxidant synthesized by the human body and is found in every cell, helping convert glucose into energy. It is a good antioxidant, which neutralizes free radicals that affect cells and lead to aging diseases. However, the beneficial effects of alpha lipoic acid on cataracts, multiple sclerosis, Alzheimer's disease and heart attack are still being discussed and are needed more extensive studies on it.

Practical application 9.5

Complete the table with characterization of some dietary supplements containing fatty acids and phenols, prebiotics, probiotics, lutein, coenzyme Q ,that have been found in the pharmacy, according to the examples in The Practice Guide: ***1 example of product for each nutraceutical.***

Product name	Composition Content of active ingredients	Sources of obtaining	Pharmacological effect	Indications for use	Specific recommendations
Bifilac caps. gran/sus. oral	Streptococcus faecalis Clostridium butyricum Bacillus mesentericus Lactobacilus sporogenes	Lactobacili	It antagonizes the activity of pathogenic microorganisms, stimulates immunity and repair processes	Prophylaxis and treatment of dysbacteriosis	Caution in children with compromised intestinal mucosa

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CHAPTER 10.

PHARMACEUTICAL FORMS WITH CONVENTIONAL AND MODIFIED RELEASE

Authors: Eugen Diug, Nicolae Ciobanu

OBJECTIVES

The student must know the prosses of drugs manufacture in pharmaceutical industry and, based on the theoretical knowledge accumulated in the disciplines, Industrial pharmaceutical technology, Biopharmaceutical and pharmacokinetics, he must be able to interpret the principles of formulation, the properties of the auxiliary substances, the reasoning of selected auxiliary substances, preparation, the bioavailability of drug substances from different pharmaceutical forms, and the important pharmacokinetic parameters for optimal pharmacotherapy. To know the influence of the formulation and manufacturing methods on the quality of the pharmaceutical form and which will determine the type of recommendations that the patient has to offer, regarding the use / application, therapeutic effect, preservation mode, validity.

It is necessary for the student to be able to coordinate the treatment and medication indications with the preparation method and the properties of the pharmaceutical form. Examples: the recommendation of a fast-acting pharmaceutical form for the systemic treatment of an acute symptom (migraine, insomnia) or a prolonged-release drug (single administration within 24 hours), if the drug has a short biologic half-life, which would requires repeated administration at small intervals, or the recommendation of an antibiotic ointment in superficial skin infections, and to ensure skin absorption the recommendation of a transdermal therapeutic system or a O/W type emulsion, etc.

Evaluation of the preparation of pharmaceutical forms (solutions, ointments, suppositories, capsules or tablets with rapid, prolonged or controlled delivery, etc.) regarding the technology used, the machine and the product characteristics.

According to the method of disposing of pharmaceutical substances from the pharmaceutical form, we distinguish:

1. Conventional pharmaceutical forms
2. Modified forms and pharmaceutical systems

1. CONVENTIONAL PHARMACEUTICAL FORMS

This category includes: peroral drug solutions and applied to the skin and mucous membranes; syrups; aromatic waters; extractive solutions and extracts; parenteral solutions; aerosols; emulsions; suspensions; semi-solid preparations (ointments, gels, creams); suppositories; powders for internal and external use; granules; capsules; tablets.

Practical application 10.1.

In the practice notebook, describe one product, of choice, of each pharmaceutical form according to the following model (examples):

N	Pharmaceutical form, packaging	The trade name of the product, manufacturer	IDN of drug substance (s) quantity per pharmaceutical unit (dose)	Auxiliary substances used in formulations	The role of each component in the formula	Pharmaco-therapeutic group and ATC code. Bioavailability (BD)%; pharmacokinetics
1.	***Rectal suppositorie, blisters N 6 x1***	**Feloran,** *Sopharma, (Bulgaria)*	Diclofenac sodic, 25 mg	-	Active substance	Non-steroidal anti-inflammatory and antirheumatic; M01A B05; M02A A15.BD rel. – 98,3 %; V_d - 0,12 – 0,17 l/kg; $T_{max.}$ – 1 hour.
The stages of the technological manufacturing process: 1). Monoglycerides and tristearate sorbitan melt at a temperature of + 550 C; 2) to the molten mixture add diclofenac sodium and aerosil and mix for 15 minutes; 3) cool				Suppocire CM Suppocire	Monoglycerides - suppository base Monoglycerides	

N	Pharmaceutical form, packaging	The trade name of the product, manufacturer	IDN of drug substance (s) quantity per pharmaceutical unit (dose)	Auxiliary substances used in formulations	The role of each component in the formula	Pharmaco-therapeutic group and ATC code. Bioavailability (BD)%; pharmacokinetics
to + 500 C and packaged in N 6 thermoformed blisters, welded and packed in a cardboard folding box.				AS2X	- suppository base	
				Crill 3	*Sorbitan tristearat* - tensioactiv	
				Aerosil	Thixotropic action	
2.	***Capsule, blister,*** *N 10; 1 blister in cardboard folding box*	**Feldoral,** *SEDICO, (Egypt)*	Piroxicam, 20 mg	-	Active substance	Non-steroidal anti-inflammatory and antirheumatic, M01A C01; M02 TO A07. Vd - 0.14 l / kg; Tmax. - 3-5 hours; t50% - 50 hours; Cmax. = 1.5 - 2.0 µg / ml
The stages of the technological manufacturing process: 1. Piroxicam, lactose and wheat starch are mixed in a low-humidity mixer until homogenized. 2. The obtained mixture is pressed in lighters that are crushed, passed through the screen to obtain uniform granulate. 3. Magnesium stearate is added to the granulate and sodium lauryl sulfate is stirred for 10-15 minutes. 4. The granulate is conditioned in hard capsules. 5. The capsules are packed in 10 blisters and a blister is placed in a cardboard folding box.				Lactose	Thinner	
				Wheatstarch	Disintegrating	
				Magnesiums tearate	Lubricant	
				Sodium lauryl sulphate	Anionic surfactant, moderate lubricant	
3.	***Ointment,*** 15 g, aluminum tube; N1, folding cardboard box	***Dermafluci n N,*** Farmaprim SRL (Republic of Moldova)	Fluocinolone acetonide -0.25 mg / 1 g; Neomycin sulphate - 5.0 mg / 1 g.	-	Active substance	*Corticosteroids in combination with antibiotics. D07CC02. Prepared with topical action*
The stages of the technological process of manufacture: 1. In the reactor (temperature 60- 65°C), the petroleum jelly and the lanolin are successively melted to which the petroleum jelly is added and homogenized for 20-60 min. The mixture is subjected to a gradual cooling process to a temperature of 40-45°C. 2. Add the neomycin sulphate to the mixture and mix for 10-30 minutes (mixture 1) 3. In a preparation vessel heat the propylene glycol to 40-45°C, to which is added fluocinolone acetonide, the mixture homogenize for 15-30 min. until complete dissolution (mixture 2). 4. To mixture 1 add mixture 2 and mix for 60 minutes. then cool to 36-40°C. 5. The ointment obtained is packaged in 15.0 g aluminum tubes and packed in a cardboard folding box.				Propylene	Solvent	
				Vaselineoil	Hydrocarbon, Adjusting the viscosity,	
				Anhydrousla nolin	Dispersion agent Hydrophobic excipient, Emollient	
				WhiteVaselin e	Hydrophobic excipient, hydrocarbon, thixotropic action	
4.	***Tablets, blister*** Nr. 10; N1; N2 or N10, folding cardboard box	***Ampicilin-RNP,*** RNP Pharmaceuticals PLC*(Rep. Moldova)*	Ampicillin trihydrate, 250 mg	-	Active substance	Beta-lactam antibiotic. Semi-synthetic penicillin with a wide range of action. J01 CA01 Tmax. - 1-2 hours;

N	Pharmaceutical form, packaging	The trade name of the product, manufacturer	IDN of drug substance (s) quantity per pharmaceutical unit (dose)	Auxiliary substances used in formulations	The role of each component in the formula	Pharmaco-therapeutic group and ATC code. Bioavailability (BD)%; pharmacokinetics
						t50% - 0.7 - 1.5 hours; BD - 30-55%.
Stages of the technological process of manufacture: 1. In the mixer mix the microcrystalline cellulose with the ampicillin trihydrate for 20-30 minutes, to which is gradually added the corn starch, the magnesium stearate and the talc, the mixture is continued until a homogeneous mixture is obtained. 2. The mixture is subjected to the compression process. 3. Tablets numbering 10 are placed in blisters. 4. 1, 2 or 10 blisters are packaged in a folding carton.				Micro-crystallinecellulose	Thickener,	
				Cornstarch	Flowingagent	
				Magnesiumstearate	Disintegratingthinner	
				Talcum	Lubricating	

2. FORMS AND PHARMACEUTICAL SYSTEMS WITH MODIFIED RELEASE

Depending on the principle of disposal of the drug substance and the place of administration, the modified release pharmaceutical forms and systems are classified in:

Drugs with rapid dissolution or disintegration in the oral cavity (orodispersible tablets, Eur. Ph.) Tablets that dissolve in the oral cavity from a few seconds to 3 minutes without using water, intended for systemic action - examples: Zyprexa®VeloTab ™ (Olanzapine, 10 mg, tablets);

Prolonged-release drugs:

- **Zero Order Release system.** This type of release provides a constant rate of release of the active substance over a well-defined period of time. This technology is primarily used for drugs with a short biological half-life to maintain plasma concentration in the area of therapeutic concentrations for as long as possible.

Examples: DilacorXR® - diltiazem - Ca ++ ion channel blocker - antihypertensive / angina pectoris. Capsules containing micro-tablets with extended release for 24 hours: 60 mg; 120 mg; 180 mg and 240 mg. (prod. Watson Labor. Inc., USA).

- **Binary Release System**. The system provides for controlled disposal of two different drug substances in a single formulation.

Example: Madopar – DR, "Roche" Switzerland; Levodopa 200 mg + Benserazid 50 mg; (the treatment of parkinsonism).

- ✓ ***Quick-Slow Release System***. This formulation initially provides for a rapid, immediate release of the active substance, followed by a constant rate of yield over a certain period of time. Examples: 1. Diclofenac – Ratiopharm – uno. Total dose 150 mg: 25 mg is released immediately; 125 mg is slowly released; 2. Ritalin LA ® (Methylphenidate hydrochloride) formulation with controlled release of central nervous system stimulants to treat attention deficit hyperactivity disorder (ADHD) in children. From the initial capsules there is an immediate release from uncoated microgranules and then the controlled release from film-coated microgranes takes place.

- ✓ ***Slow-Quick Release System***. This type of formulation initially provides for a constant rate of release of the drug substance followed by a rapid, immediate cessation at a certain time interval. Example: SULAR ® (nisoldipine) slow-release tablets The tablets consist of outer shell and core. Both constituents contain nisoldipin. The coating slowly releases the active substance, and the core contains a fast-release formulation. The doses are 10, 20, 30 or 40 mg and are given every 24 hours.

- **Positioned Release System drugs.** Formulation in these cases involves locating the tablet in a certain portion of the digestive tract (colon) and then releasing the active substance from the system. Example: XATRAL SR, 10

mg prolonged-release tablets located in the colon. The active substance - Alfuzosin - antagonist of 1 alpha receptors. It blocks the alpha receptors in the prostate muscles. It is used in the treatment of benign prostatic hypertrophy. Manufacturer of the company Sanofi Aventis (France). Prolonged gastric retention medications (float systems: tablets with: Furosemid; Ciprofloxacin; Captopril; Verapamil; Atenolol; Cinarizine; Diltiazem; Nimodipin; Theophylline; capsules with: Nicardipin; Furosemid; Misoprostal; Diazepam; Propranolol; microsafre; ibuprofen.

- **Accelerated Release System.** The system provides for a constant accelerated release of several doses of the active substance. Example: Indomethacin-containing capsules in the form of pellets obtained by extrusion and spheronization. The pellets are coated with microporous membranes that control the release of MS.
- **Circadian (chronically-releasing) drugs**. (Chrono oral Drug Absorption system) - "Geoclock". The chrono-system releases the active principle after a well-determined time, called "lag time". It is used for the treatment of rheumatoid arthritis to reduce morning pain. Example: For this purpose by the company "Nitec Pharma" using the "Geoclock" technology SkyePahrma the system with prednisone content "Lodotra" was developed. MS is rapidly released from the core of the tablet more than 4 hours after ingestion. It reduces the nocturnal secretion of endogenous cortisol thus reducing the inflammatory effect (morning pain).
- **Delayed Release System. Example:** Protonix Delayed Release Tablets (pantoprazole sodium, proton pump inhibitor) reduce the amount of acid in the stomach, approved for short-term treatment, by up to eight weeks of erosive esophagitis associated with gastroesophageal reflux.
- **Multiple Pulse System Drugs.** The systems are formulated so that the active substance is initially released immediately, shortly, for rapid action, followed by the latent period and after that a second rapid release and so on. Tablets of this type are intended to contain drug substances with certain side effects, such as appetite suppressants (Phendimetrazine), to minimize these actions during certain periods of time during the day, especially during meals.

Controlled Delivery Medications.

Duration of therapeutic effect: several days or weeks; a few months or a few years. It is classified in: systems with pre-programmed transfer; physically or chemically activated systems and systems with self-regulating or feed-back failure.

- **Systems with pre-programmed failure**. They consist of: reservoir with drug substance; energy source (mass transfer is generated by the existence of a concentration gradient as a result of molecular diffusion); element that controls the release of the active substance from the tank.
  - ✓ with local action (for ophthalmological use: Pilo 20; Pilo 40; for gynecological use: intrauterine system "Mirena");
  - ✓ with systemic action: transdermal absorption (therapeutic systems with: estradiol, clonidine, nitroglycerin, scopolamine, nicotine, lidocaine, fentanyl, capsaicin, etc.).
- **Activate Activated systems:** by osmotic pressure ("OROS" systems: Procardia XL (nifedipine) "Pfizer". Oral tablets in angina / hypertension); by magnetic field; iontophoresis - intensification of the drug flow, under the influence of an electric field for activating the transport of molecules of a drug substance ionizable through a biological membrane (the skin). Electricity flows through the solution containing ionized drugs. systems with self-regulating or feed-back failure, insulin implantable pumps;
- **Bio Bioadhesive systems** (mucoadhesives), compressed with: Metronidazole; clotrimazole; acyclovir; verapamil; Lactoferrin.

Drugs vectored or with delivery to the target: Vectorization (transport to the target) implies: the realization of the maximum potential activity of the drug substance; optimizing availability in the vicinity of specific pharmacological receptors; protecting both the drug substance and the body.

Drug carriers: microparticles, nanoparticles, liposomes, virosomes, nioosomes, monoclonal antibodies (examples of ACM: RITUXIMAB (rituxan) - treatment of non-Hinjingian lymphomas; CETUXIMAB (erbitux) - in colorectal cancer; TRASTUZUMAB (herceptin) - in treating cancer patients has excess HER 2 receptors on the surface of the malignant cell.

Practical application 10.2.

In the practice book, write a product, found in the pharmacy, of each group of medicines with modified delivery and transport to the target according to the following model (examples):

Nr.	Pharmaceutical form, packaging	The trade name of the product, manufacturer	IDN of drug substance (s) quantity per pharmaceutical unit (dose)	Auxiliary substances used in formulations	The role of each component in the formula	Pharmacotherapeutic group and ATC code. Bioavailability Tea (BD)%; pharmacokinetics
1.	Tablets With **slow-fast delivery**	***SULAR*®** SkyePharma Production SAS (France)	***Nisoldipine, 40 mg***	-	Active substance	Ca ++ ion channel blocker; BDabs. about 5%; Tmax. = 9.2 hours; t50% = 13.7 hours It is given once in 24 hours.

The core of the tablet consists of ½ of the dose of nisoldipine, hydroxypropyl cellulose, lactose, wheat starch, crospovidone, sodium lauryl sulfate, povidone and magnesium stearate. Due to crospovidone and sodium lauryl sulfate the nucleus is rapidly disaggregated. The tablet film consists of ½ of the dose of nisoldipine, hydroxypropylmethylcellulose, polyethylene glycol, iron oxide and titanium dioxide. Hydroxypropylmethylcellulose contributes to a slow, controlled release of the active principle, due to the formation of a gelling layer on the surface of the tablet.	Hydroxypropyl cellulose	Binder used for wet granulation	
	Lactose monohydrate	Thinner, higher dissolution	
	Wheat starch	Thinner, binder	
	Crospovidone	Superdezagregant	
	Microcrystallinecellulose	Disintegrating, high compressibility	
	Sodium lauryl sulfate	Surfactant, solubilizing	
	Povidone	Agglutinant	
	Magnesium stearate	Lubricating	
	Hydroxypropylmethylcellulose	Hydrophilicfilmmaker	
	Polyethylene	Plasticizer	
	Ironoxide	Dye	
	Titandioxide	Dye	

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Chapter 11.

TECHNICAL-MEDICAL PRODUCTS.

Authors**: Mihail Brumărel, Stela Adauji, Liliana Dogotari**

In pharmaceutical practice, next to the existing medical preparations in more or less modern traditional pharmaceutical forms, technical and medical products occupy a considerable importance. There are some products which are intended for the treatment of some affections, especially at the skin and membrane level, others are intended for diagnosis and monitoring, other for protection and prevention, etc.

The products, besides the medicines that can be stored and released by pharmacies, are:

1. Medical devices for individual use, including consumables for these, with the exception of implantable medical devices
2. Medical diagnostic devices in *vitro,* intended for consumers (self-testing devices)
3. Materials, articles and accessories needed to care for the sick people or the elderly
4. Articles and accessories used in the application of medical treatment or in the medicines administration
5. Intended products for the maintenance or application of eye contact lenses
6. Medicinal plants and derivatives products , essential oils
7. Articles and appliances used in oral and / or bodily hygiene
8. Dietetic products and special articles or accessories necessary for their use
9. Cosmetic products for body care
10. The insecticide and acaricide are intended for an applicable human
11. Food supplements
12. Acoustic protection equipment
13. Childcare products, such as feeding botle, pacifiers, sterilizers, nipples, milk powder, etc., except articles of clothing, shoes, furniture, strollers, children's books, toys, stationery, detergents
14. Products for sexual protection.

According to the law nr. 92 since 26.04.2012 „Regarding medical devices", the terms and expressions below are defined as follows:

medical device –instrument, apparatus, equipment, material or other article, used separately or in combination, including the computer program intended by its manufacturer to be used specifically for diagnostic and / or therapeutic purposes and necessary for the proper functioning of the medical device, intended by the manufacturer to be used for humans for the purpose of:

- ✓ diagnosis, prevention, monitoring, treatment or amelioration of an affection; ;
- ✓ diagnosis, prevention, surveillance, treatment, improvement or compensation of an injury or disability;
- ✓ investigation, replacement or modification of the anatomy or of a physiological process;
- ✓ conception control,
- ✓ and that does not execute the basic actions envisaged, uman in / or on the human body, by pharmacological means, immunological or metabolic, but whose function can be assisted by such means;

active medical device – medical device whose operation is based on a source of energy electricity or any source of power ***other*** than that generated by the human body or gravity;

active implantable medical device – active medical device intended to be introduced , totally or partially,through medical and ***surgical*** interference, and remain implanted in the human body or in its orifice;

accessory – the article that is not a medical device, has intention in particular to be used with a device to allow its **use** in accordance with the offered aim by the manufacturer;

medical **device** for vitro diagnostic – medical device which is a reagent, reaction product,calibrator, material control, kit, instrument, apparatus, equipment or system, used separately or in combination , intended by the manufacturer for being used in vitro **for** examining samples, including donated blood and tissues , being derived from the human body , exclusive or main, for the purpose of obtaining some information:

- ✓ regarding the physiological or pathological condition or a congenital anomaly;
- ✓ to determine the safety and compatibility with a potential recipient;
- ✓ for monitoring therapeutic measures.

The sample receptacles are considered medical devices for in vitro diagnostics. The sample receptacles are vacuum devices or not, intended by the special manufacturer for the initial preservation and

preservation of ***samples*** obtained from the human body, for the purpose of an invitro diagnostic examination;

individual device on order – medical device, made on purpose of qualified doctor, that under his responsibility develops structural descriptions of the intended device for a concrete patient. A recipe also can be given to any other person authorized on the basis of his professional qualification. The medical device in series that must be adapted to the concrete requirements of qualified doctor or other authorized person is not considered personal ordered device.

device for clinical investigation – the device intended to be used by the qualified medical practitioner when he conducts the clinical investigation in an adequate clinical environment. For the achievement purpose of the clinical investigation, any other ***person*** who, by virtue of the professional qualification he is authorized on prosecuting such inquiries and will be confessed by equivalent to the qualified doctor.

By the order of Ministry of Health of the Republic of Moldova nr. 959 from 01.10.2012 . „Regard to insurance access of population to medications and medical wares of social importance" an obligatory list is regulated:

Plasters	Syringe
Bacterial plasters	Insulin syringes
Pepper plaster	Alcohol-soaked towels
Compression bandage	Mustard plaster
Tourniquet band	Infusion systems
Nester rubber gloves	Termophor
Sterile rubber gloves	Thermometer
One-use mask	Cotton wool
Enema	Medical cotton roll
Dropper	

From the great number of the mentioned medical devices in pharmacies, often there are the next categories of devices and medical technical wares:

- ✓ device for parenterally introduction of medications
- ✓ bandages and curative plasters
- ✓ diagnostic devices of in vitro
- ✓ sexual protection products and devices for contraception
- ✓ childcare products

A. DEVICES FOR PARENTERAL ADMINISTRATION OF MEDICINES

The most important medical devices used for parenteral administration are:

- ✓ different syringes
- ✓ short and long catheters; peripheral and central
- ✓ infusion kits
- ✓ transfusion kits

Syringe

The syringe is composed of a cylinder and a piston ring to the cylinder with which the drug substance is injected. The syringe must be sterile, can be manipulated and presented or corrected to ensure an exact dose. There are two types of syringes:

- ✓ *Two-component syringe*: consisting of material of syringe (transparent cylinder), with connection Luer slip (standard) or the connection Luer lock, having a centered or eccentric cone.
- ✓ *Syringe with three components:* In addition, it has a connecting device made of an elastomer.

The syringes with special uses are:

- ✓ serynge Guyon used in ORL for auricles or in Urology, having large capacities. 100-200 mls;
- ✓ preliminary filled syringes with the capacity of 0,5 - 1 ml, with small quantities of substances are introduced into the body requiring a very exact dosage (heparin, insulin, interferon, vaccines, etc.).
- ✓ PEN devices for insulin administration, accordingly PEN of device without a needle, these are provided with the special tip that provides penetration of medicinal substance through a skin with high-rate and pressure, without the necessity of the use of needle.

The syringe needle consists of:

- ✓ needle adapter – the part that is connected to the syringe
- ✓ the bevel – the angled surface formed on the tube when sharpened to make a needle point. It is cut

obliquely, by sharpening in three planes and can be long or short, with variable opening, suitable for the types of punctured tissues.

The exterior diameter of the needle or nominal diameter is expressed in Gauge (G) and is colored in different colours

Chart 11.1.

Colour classification of needles for syringes

Colour	(G)	Needle diameter (mm)
Rose	18G	1,2
Pale yellow	19G	1,1
Yellow	20G	0,9
Green	21G	0,8
Gray	22G	0,7
Blue	23G	0,6

Catheters are used for the administration of drug substances or for functional explorations and can be:

- ✓ *peripheral venous catheter,* necessary for intravenous administration, by injection or infusion, or in the case of transfusions. To ensure continuous or intermittent administration through a placed catheter i.v. without the need for repeated pricking.
- ✓ *central venous catheter, used for the administration of medicinal substances* , fluids, nutrients or blood products for a rapid effect or for long periods and in large volumes, but peripheral catheterization is impossible.

Gravitational infusion kits contain**:** medical perforator or drill, air filter, drop counting chamber having a particle filter, flow regulator, tube approximately 150 cm in length and cone-shaped terminal Luer or, preferably, Luer-Lock.

Transfusion kits are intended for the collection, transfer and transfusion of blood and its derivatives. It presents the following differences compared to infusion devices: în general, the perforator is not equipped with an air filter which always has a blood filter that is located in the counting drop chamber or in a filtering chamber.

B. DRUGS AND MEDICATION PLASTERS. BIOFILMS

Bioadhesive **plasters** are non - medicated articles released in pharmacies. The articles consist of an adhesive excipient spread in thin layer, continuous or discontinuous, on a suitable support and are intended to isolate or protect healthy or damaged skin from the external environment. The support of the colemplasters may or may not be impermeable or permeable to water and air vapors; in general it can be colored pink or has a skin color.

The main purpose of colemplasters usage is: bandages fixation, skin protection, suture sores and skin support in allergy.

The bioadhesive bandage and **plasters** are parapharmaceuticals made up of a stamp, on which a bandage material is fixed, which may be: hydrophilic cotton, wool, hydrophilic viscose or other suitable material, intended to isolate or protect healthy skin or harmed, by the external environment. Those applied to wounds, open wounds must be sterile. If the bandage material is impregnated with a drug substance, we are talking about **drug plasters** or patches. Antiseptics, keratolytics and antirheumatic agents are most used as medicinal substances. Sometimes the drug substance is incorporated into the adhesive mass used for fixing. The plasters are packaged individually or in strips that are cut at the time of use. They are intended for application on small skin lesions, for local treatment.

Bioadhesive films are also called biofilms. They are solid or transparent preparations, made of synthetic polymers. They are based on the film-forming raw materials, which have the role of protecting and isolating the wound

- ✓ non-medicated *bioadhesive films* based on polyurethane are transparent, in the form of thin sheets, stretchy and supple, transparent to light, behaving like a double skin. They are permeable to air, oxygen, water vapor, but impermeable to germs. One of their surfaces is covered with an acrylic adhesive layer, which allows the dressing to be fixed on the dry skin. They are indicated as a replacement of the skin in acute and chronic superficial wounds, in the epithelialization phase, in the recovery of the surgical wounds in the field of plastic surgery, in the treatment of superficial burns and for fixation of the catheter;
- ✓ *Adhesive biofilms* formed in situ are adhesive "bandage" solutions based on methacrylates, placed in

pressurized containers, intended for spraying on wounds, burns or sutures. After evaporation, the solvent forms a protective film at the site of application. They are used especially in the case of first aid, for the treatment of wounds and burns.

Transdermal therapeutic systems (STT) are controlled-pharmaceutical forms that allow the skin to administer drug substances intended to exert systemic action. Also called transdermal plasters. According to the 2004 Supplement of FR X transdermal plasters are flexible pharmaceutical preparations, of different sizes, containing one or more active substances. They are intended to be applied on intact skin, in order to release the active substance into the systemic circulation after they pass through the skin barrier. Given that STTs are considered drug preparations and not medical devices, some details on them were presented in Chapter III. 7.

C. MEDICAL DEVICES FOR IN VITRO DIAGNOSIS

From the category of products and devices for functional exploration intended to investigate the human body, to know his normal or pathological state, thermometers, tensiometers and glucometers are the most commonly to find them in pharmacies.

Thermometers

According to the Directives of European Community, mercury thermometers were taken off from from pharmaceuties. However there are the alternative decisions already tested and applied. Some manufacturers use a liquid alloy of gallium, indium and tin (**galinstan)** as a substitute for mercury. By other alternatives to the mercury thermometer, intended to measure temperature of human body, are: thermometers with liquid crystals, for measuring body temperature and infrared thermometers, with a higher measurement speed.

Different types of thermometers encountered in pharmacies:

- ✓ Pencil Type Digital Thermometer
- ✓ *Mosen Baby Thermometer*
- ✓ *Forehead Ear Thermometer*
- ✓ *Digital Flexi-head Clinical Thermometer*
- ✓ Boso Therm Flexible Tip Digital Thermometer
- ✓ *Infrared Thermometers*
- ✓ *Color Changing Thermometer*
- ✓ *Patch thermometer*
- ✓ *Magnetic Strip Thermometer*

Tonometer

There are several methods for measuring arterial pressure, some invasive and others non-invasive. They are based on ultrasonic, oscillometric and flush methods. The devices intended for measurement of arterial pressure (tensiometers) are sold in pharmacies and not only, are several types of them:

- ✓ aneroid sphygmomanometer based on the method of auscultation;
- ✓ semi - automatic tensiometer, based on the oscillometric technique;
- ✓ automatic tensiometer, based on the oscillometric technique;
- ✓ for the arm;
- ✓ for the wrist;
- ✓ for the finger.

Blood Glucose monitoring device (glucometer)

The principle of glucometers work is based on the determination of maintenance of blood glucose from capillary blood on the enzymatic action of glucose oxidase in test strips. The result of this action is recorded by the glucometer biosensor and represented on its screen.

Types of glucometers:

- ✓ glucometers on which the sample of blood is applied on the inside tape of medical device
- ✓ glucometers on which the sample of blood is applied on the outside tape of medical device
- ✓ with the tests fixed in a cartridge that is attached to the device and completely changed after emptying

The systems of continuous subcutaneous administration of insulin (CSII- Continous Subcutaneous Insulin Infusion, Insulin pumps) are based on the continuous release of insulin to ensure the basic level of this substance throughout the day , as well as on bolus release before or during the meal. The pump can be programmed for the needs of each patient, ensuring an individualization of the therapy. The

insertion of vascular models provide easy monitoring of blood glucose levels.

The component parts of the system of continuous subcutaneous administration of insulin are: the pump, the cannula which may have different insertion angles, the device for subcutaneous crimping and removal of the cannula. These products fall into the category of medicines.

D.PRODUCTS FOR SEXUAL PROTECTION AND CONTRACEPTION

The protection from venereal diseases can be provided with different barrier methods that render a contraceptive action also. The use of these methods includes:

- ✓ condom (male and female)
- ✓ vaginal diaphragm
- ✓ dome or cervical diaphragm
- ✓ contraceptive vaginal sponge

The contraception can also be realised by applying locally spermicides or by using intrauterine devices (IUDs), but these methods also do not provide protection against sexually transmitted diseases.

The male condom is a closed cylinder at one end consisting of a latex foil or biopolymer that is applied to the erect penis before sexual intercourse. Male condoms can be pre-lubricated with spermicide, which is more effective as a contraceptive method than those without spermicide. Condoms are conditioned and packaged separately. The condom should have the date of manufacture and the expiry date on the packaging. When the condom is used, it should be taken into account the possibility of accidents, such as breaking or slipping.

The female condom is made of polyurethane and is similar to the male condom, with a larger diameter. It is a cylindrical tube that presents at the two ends two rings, one flexible at the closed end, which will be placed in the vagina, and a larger one, located at the open end, which will remain in the vulva covering the genital area of the woman and the penis. It can be inserted 8 hours before sexual contact, but must be removed immediately after it.

The diameter of the **vaginal diaphragms** varies from 50 to 105 mm. It can be associated with a spermicide by applying it on both sides of it. It is contraindicated in the first 6 weeks after birth and in the case of repeated urinary infections prior to the use of the diaphragm. The diaphragm can be inserted a few hours before sexual contact and left at least 8 hours after sexual contact (but not more than 24 hours) to allow the sperm to immobilize.

The cervical domes are similar to the vaginal diaphragm, but have smaller dimensions, from 22 to 50 mm. It is placed on the cervix and in this way ensuring its coverage. It has no circular metallic ring. May be associated with a spermicidal gel. It may be kept in the vagina for several days. Requires initial fixation by a qualified person and does not provide protection against sexually transmitted diseases.

The contraceptive sponge is made of polyurethane, has a round shape with a diameter of 5.5 cm. and is impregnated with a spermicide. It is indicated in the case of women who have a short sex life. The contraceptive sponge can be kept for 24 hours.

Spermicides are substances that cause immobilization and inactivation by sperm destruction in the vagina. Non-oxynol, octoxinol, chlorhexidine incorporated in inert and processed excipients are commonly used as spermicides: creams or gels, vaginal suppositories, foams (sprays), foam tablets, water-soluble films. Used alone as a contraceptive method, they have a high failure rate.

Intrauterine devices (IUDs) are small (2.5 - 3.5 cm) and flexible, made generally of polymeric material. Flexible or stainless steel (inert IUDs), having copper sheets or wires (active IUDs, copper) or having a reservoir that constantly releases a progestogen (hormone-releasing IUDs). Almost all types of IUD have attached one or two strands that remain in the cervical canal, extending into the vagina. Sterilization exerts its contraceptive effect by preventing the meeting between the sperm and the egg, hindering sperm movements in the female genital tract, preventing the implantation of the egg in the uterus (in the case of hormones preventing the production of ovulation).

Types of intrauterine devices (IUDs):

- ✓ *Inert sterilizers* can be made of polyethylene, having in their composition also a contrast substance.
- ✓ *The active* copper grooves are T - shaped, with copper wrapped in the form of a wire (200 mm2) on the vertical arm of the T. To prevent thread fragmentation, the T-Cu 200 Ag model has a copper wire core made of silver.
- ✓ *Therapeutic systems* with applications in gynecology are drug preparations with contraceptive effect,

described in Chapter III. 7. They are better known:

- ST "Progestasert", contraceptive with progesterone
- ST "Nova-T", an intrauterine device with levonorgestrel
- ST "Mirena", an intrauterine device with levonorgestrel.

Merchandising analysis and its role in assessing the quality of the products.

A method of scientific study of the goods, which consists in the imaginary division of the product into the constituent elements for the multilateral study of the quality of the product and the appreciation of its innosense is represented by the **merceological analysis.**

The merchandise analysis is performed for the pharmacist to determine the optimum assortment for the products for the pharmaceutical products, the medical-sanitary institutions, as well as receiving the products according to the quality and quantity.

Organoleptic methods are often used because time is limited in the process of receiving products.

From the above, it appears that the merchandise analysis is a preliminary stage for identifying the products: *counterfeit or non-qualitative.*

The movement of goods represents the process of movement of the goods from the manufacturer through the wholesale and / or retail trade to the consumer.

The merchandise analysis consists of several basic stages:

1. the selection of products for analysis;
2. the selecting of consumer properties and technical indicators, which will be analyzed;
3. the analysis of consumer properties and technical indicators.

When is performed the merchandise analysis by the *organoleptic method*, the following *steps* are:

■ *Determining the classification group and subgroup* (based on the data about the destination of the goods, consumer properties, production methods, abroad, etc.).

■ *The determination and deciphering of goods codes:*

✓ the determining and the deciphering digital codes according to general codes;

✓ the determination and the decryption of barcode on packaging and recipient

■ *Determining the type of product, the trade name.*

✓ the study of the external appearance of the product:

- *for medical equipment, tools, number of pieces* , the character of the connection of the pieces, the type of lock, the character of the curvature of the working part: horizontally or vertically, the type and number of cog , etc .;
- for drugs: pharmacotherapeutic group, composition,medicine form, etc.

✓ the determination of geometrical sizes and characteristics of the product type:

- for medical technique , instruments: length, width, height, diameter, capacity, etc .;
- for drugs: number, weight, dosage, quantity of units of the drug form, etc.

■ *Determining the technique characteristics of the product.*

✓ determining the material from which the product or component parts are made;

- For medical equipment: metal or alloy - hotel, copper; polymer, rubber, glass, etc .;
- For medicines: active substance, other components;

✓ determining the method of producing the product;

■ *The receiving of goods in accordance with the requirements of the technical documentation of standardization.*

✓ the evaluation of exterior appearance.

- *for medical products (equipment, tools):* the measurement of product and the determination of presence of the component parts and the absence of impermissible defects, scratches, cracks, the uniformity of the protective layer, traces of corrosion, mechanical deformation, etc .;
- *for medicines: the color of tablets or solutions, the lack of precipitate, the inclusion in solutions, the lack of primary defects of packing etc .;*
- *for other products:* the measurement of the product, the measurement of the presence of the component parts, the lack of inadmissible effects (cracks, traces of aging, extraneous inclusions).

✓ The evaluation of external appereance. The evaluation of component

- for medical technology, tools: the determination of component parts and accessories.
- for medicines: the determination of the matching quantity of medicines in the primary, secondary packaging,

the presence of accessories, ej., blades for opening the ampoules, etc.

- ✓ The evaluation of functional products.
- *for medical technology, instruments:* the determination of matching functionality, according to the technical documents (operation in different regimes, cutting, elasticity, durability, etc.)
- *for medicines:* authenticity; spraying, for aerosols, etc.
- *for other products:* the determination of indicated functionality in the technical documentation (syringes - flow; suture material - durability, equal diameter throughout; bandages - hygroscopicity, etc.).

■ *The evaluation of the pack*

- ✓ determining the presence of the primary, secondary, collective, transport packaging;
- ✓ the external evaluation of the quality of the package (smooth, non-deformed surface);
- ✓ the evaluation of the protective, consumer, aesthetic properties of the packaging;
- ✓ determining the presence of protective oil on products (for tools or equipment), the presence of parchment or paraffinized paper, etc.

■ *Evaluation of the marking products.*

- ✓ determining the presence of the marking on products (devices, medical instruments, sanitary - hygienic products, etc.), its deciphering, the appreciation of the correspondence of the documentation requirements;
- ✓ the evaluation of the marking correspondence on the package of all types of technical requirements;
- ✓ the determination of the utility of goods according to the validity of a period (sterility, warranty period).

■ *The organization and evaluation of the correctness of the storage and transport of the products.*

- ✓ the determination of group of storage in accordance with the order of MH RM Nr. 28.
- ✓ the determination of rightness of conduct in accordance with the position of order.
- ✓ if need be, recommendations on the repeated preservation (for surgical instruments) and the transportation of the estimated products.

■ *The choice or recommendation of methods disinfection and sterilization (if necessary).*

■ *The control of accompanying documents for the purpose the rightness of filling.*

■ *The perfection of reception act of products in quality of amount.*

Practical application 11.1.

You have to present the analysis of 2 technical-medical products in writing form, encoutered in the pharmacy during the practical practise and you have to mention what recommendation should be given to patients
Mention the types of medical thermometers found in the pharmacy
Describe one determination device of a blood glucose or blood pressure

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CHAPTER 12.

EMERGENCIES IN PHARMACY.

Authors: **Corina Scutari, Ludmila Anghel**

Emergency includes situations in which life or one of the vital functions of the organism is threatened and which immediately requires the intervention of the doctor and the transport of the patient. In his activity, the pharmacist can be confronted with situations that represent medical emergencies and the pharmacist's quick and correct intervention can save the patient's life.

Objectives

- The student must recognize the situations that represent medical emergencies and the attitude recommended in these situations. Depending on the severity of the problem, it may be necessary to request emergency medical assistance or, in less severe cases, to administer a treatment.
- It is important to know the first aid measures, which can be given to the patient until the doctor's intervention.
- The student must know the telephone numbers of the emergency medical services to which he can call in case of emergence in the pharmacy of situations that require emergency medical intervention.

Epistaxis (nasal bleeding)

- the patient sits on a chair, head slightly inclined to the back; the head should not be pushed too far back; it can cause blood to flow to the posterior wall of the pharynx and swallowing it, which can irritate the stomach and trigger vomiting; it is advisable to spit the blood that gathers in the mouth and throat, and not swallowing it.
- the nasal wings are compressed for 5-10 minutes, the patient must breathe through the mouth.
- sedatives (valerian tincture) will be administered and local haemostasis measures will be applied: digital compression on the bleeding nose, cold compresses or ice on the nasal frontal region, nasal swabs soaked with hemostatic solutions (oxygenated water, 1% solution of epinephrine, thrombin, gelaspon) and anesthetic (lidocaine), nasal aspirations.
- In mild cases nasal swabs, soaked in gelatin and saline solution (1 teaspoon of salt per 500 ml of warm water) will be made.
- if the epistaxis is due to a sudden increase in blood pressure, antihypertensive agents (captopril) will be given.
- In cases where nasal swabs are needed for more than 24 hours, antibiotic treatment will be initiated to prevent the occurrence of local infections.
- if the bleeding continues, ask medical assistance.

Wounds

- thawing of the damaged region.
- stopping of the bleeding.
- the bleeding extremity should be raised above the level of the heart, and direct compression should be performed continuously.
- tayment of the skin around the wound with alcohol solution or iodine tincture.
- washing of the wound with soap and water, antiseptic solutions (70% alcohol solution, iodine tincture, iodized alcohol.
- rivanol, oxygenated water, boric acid 4%, bromine acetate 1%).
- powders with antibiotics.
- covering the wound with sterile compresses.
- putting on the bandage (it is done by bandage with the help of a gauze band or with a band-aid).
- do not tie the bandage too tightly, not to stop the blood flow. You must feel the pulse below the bandage level.

Anaphylactic shock

- check if the person has an autoinjector with epinephrine, a substance administered to improve reactions to various allergenic factors. If its response is positive you can help to inject epinephrine. This will be done by pressing the self-injecting piston at the thigh level;
- place the person facing anaphylactic shock, on the back, on a flat surface, with the lower limbs raised (20-30 cm).
- remove or loosen any garment tightly on the body and, if possible, cover the person with a blanket. Moderate reheating by the blanket and hot water bottles at the extremities is recommended.

- ✔ In no way, you will allow the person who is in anaphylactic shock to drink any kind of liquid.
- ✔ if the patient has nausea and vomiting or bleeding, it is advisable to turn him/her on the belly to prevent the risk of aspiration.
- ✔ if the person does not breathe, cough and / or is in a state of unconsciousness, perform the procedure of CPR for 2 consecutive minutes.
- ✔ adrenaline (epinephrine) administration with vasoconstrictive and bronchodilatory effect. Adrenaline 0.05 - 0.1 mg intravenously, repeated at 1-5 min, up to 1-2 mg in 60 min.
- ✔ corticosteroids parenteral: intravenous methylprednisolone 1000 mg (corticosteroid with anti-inflammatory, anti-shock, antihistamine effect).
- ✔ lack of BP recovery requires the administration of the infusion catecholamines: isoprenaline/isoproterenol.
- ✔ urgently ask the help of specialized medical personnel even if the patient's condition improves. In case of anaphylactic shock, there is a risk of recurrence of the symptomatology.

Syncope (faint)

- ✔ place the patient in a horizontal position (dorsal decubitus) with the lower limbs raised, to restore cerebral perfusion.
- ✔ keep the airways clear.
- ✔ lengthen the clothing that is too tight, especially around the neck.
- ✔ do not allow the patient to rise too quickly from this position, as the syncope may recur.
- ✔ the patient should not be resting, sitting and should not be placed in the orthostatic position.
- ✔ in young people, without cardiovascular disease, syncope of unknown cause has a favorable prognosis and rarely requires a complex evaluation. In the elderly, syncope may be due to the interaction between coexisting disorders or the drugs used, which alter with the cardiovascular compensatory mechanisms.
- ✔ normal cardiac activity can be rapidly determined by palpation of the central pulse, ie in the carotid arteries. It should be regular and have a frequency between 60 and 100 beats / minute. Any deviation from these parameters indicates a cardiac cause of the crisis of unconsciousness and requires emergency medical examination.
- ✔ a special case is represented by the lack of spontaneous respiratory movements and / or the lack of carotid pulse, which indicates either the imminence of a cardio-respiratory stop, or even a cardio-respiratory stop. Cardio-pulmonary resuscitation maneuvers (external cardiac massage and “mouth-to-mouth” breathing) will be performed urgently until the arrival of a medical team specialized in such situations.

Seizures

- ✔ support the patient and place him slightly lying on the floor.
- ✔ remove any objects that may be struck during convulsions. Keep the airways clear.
- ✔ do not place any objects between the patient's teeth.
- ✔ lengthen the clothes that are too tight, especially around the neck.
- ✔ after the convulsions have ended, turn the patient's head to one side to prevent drowning with secretions, blood or vomiting.
- ✔ if the second crisis occurs or it is about a pregnant woman, seek emergency medical attention.

Accidents caused by physical agents

burns

- ✔ the burned surface is sprayed for 15-20 minutes with clean, cold water or covered with snow, to reduce pain and prevent edema. On large surfaces of burns apply a sterile band or clean bandage. The victim is given analgesic and sedative (allheal).
- ✔ In no case should the formed bubbles be popped. Ointments, fats, oils, dairy products or other liquids are not applied on burnt surfaces, the burn should not be applied with sodium hydrocarbon or starch. All these substances can seriously harm the patient, infect the wound, form a dense film, which leads to overheating of the affected area and aggravation of the burn and its aftermath. Usage of iodine, potassium permanganate or other dyes is not allowed on the burn. Only splashing with clean and cold water is permitted and the application of medicines specifically designed for burns (aerosol panthenol). In special cases it is possible to apply sterile napkins, sprinkled with a low alcohol solution (up to 30°C), which has analgesic and disinfectant effect.

Electric shock (electrocution)

- ✔ interrupt the power source, without touching the victim or the power source with bare hands, insulating gloves or an electrically insulating material (wood, plastic, rubber) will be used to remove the power source.
- ✔ if the victim is in a cardio-respiratory stop, the cardio-respiratory resuscitation can be attempted later, but only after the power supply is interrupted (otherwise there is the danger of electrocution of the rescuer). If spontaneous pulse and breathing are present, the victim will be placed in the safety position and supervised until the medical crew arrives.
- ✔ Minor burns can be treated locally with antibiotic creams and sterile dressing, more severe burns may require surgery to clean the wound or even skin grafts.

Heat shock (insolation)

- ✔ the affected person moves into a room, away from the sun's rays.
- ✔ remove the clothes and sprinkle with cold water, wrap in a wet sheet and ventilate vigorously to increase heat loss through evaporation. Ice packs or cold water compresses are applied on the neck, abdomen and under the arm. The affected person is placed in the lying position with slightly raised legs.
- ✔ if the patient begins to shiver, the cooling process should be slowed down, as the chills increase the central temperature.
- ✔ body temperature should be measured at 10 minutes intervals and it is not allowed to drop below 38.3 ° C (risk of hypothermia).
- ✔ no fever-relieving medicine is given.
- ✔ alcohol is not used for body rubs.
- ✔ it is not advisable to administer anything (nor the water) until its condition is stabilized.

Heat Exhaustion

- ✔ the patient is placed in a horizontal position, with the lower limbs raised.
- ✔ small amounts of lightly salted liquids, salts for oral rehydration or electrolyte-rich drinks are administered at intervals of several minutes.

Frostbites

- ✔ the patient is transferred to a heated environment.
- ✔ wrap frostbitten areas in thick coats or blankets.
- ✔ the frozen bitten limb is introduced into the water with a temperature of 34-37°C (not hotter than 40.5°C).
- ✔ ensure that the heat of the whole body is maintained.
- ✔ if the victim is conscious and not vomiting, hot (not hot) liquids may be offered.
- ✔ the patient is transported to the hospital.

Hypothermia (body temperature below 34 ° C)

- ✔ In the case of hypothermia, the first aid begins with the evaluation of vital functions (freedom of the airway, breathing, circulation) and cardiorespiratory resuscitation if necessary (the chest of the victims in hypothermia is more rigid, which makes cardiac massage more difficult).
- ✔ Restoring the normal body temperature is slow, not sudden (about 1 degree per hour) and consists of:
- passive heating: bringing the victim into a warm environment, replacing the wet clothing with dry ones and covering him/her with blankets; these measures may be sufficient in mild and medium hypothermia with temperatures above 31°C.
- active external heating: immersion in hot water (40 ° C), covering with electric blankets, wrapping in warm clothes or blankets, bags or bottles with hot water.

<u>Fractures</u>

- ✔ cover the wound and stop the bleeding.
- ✔ immobilize, as far as possible, the injured part with the help of some axles.
- ✔ Prevent blood circulation interruption.
- ✔ carefully transport the patient to the hospital or doctor.

<u>Insect bites</u>

- ✔ In the case of a bee sting, remove the bee needle by lightly scraping with the blade of a knife or nail.
- ✔ wash the area with soap and water, process with hydrogen peroxide or alcoholic solution.
- ✔ Apply a cold compress or ice bag.
- ✔ topically apply hydrocortisone ointment.
- ✔ take an antihistamine (diphenhydramine, loratadine, clemastine).
- ✔ when the puncture occurs inside the mouth cavity, edema can occur immediately with respiratory distress. In

this case it is recommended that the patient suck on an ice cube.

- ✔ In the case of a more sensitive person, it is advisable to take an anti-allergic drug or, more effectively, to inject intravenous hemisuccinate with hydrocortisone. If the sting is itchy (causes itching), you can use a mentholated ointment or a dermatological lotion, which has soothing properties. If the allergic reaction due to the sting is severe, emergency medical assistance is called.

The life of the victim depends most of the time, on the ability and speed of the person who intervenes in the first aid.

Although medical problems that require emergency intervention are not common in the pharmacy, however, in the event of their occurrence, there is not much time available to search for the necessary information.To effectively intervene, the pharmacist's knowledge and skills are particularly important. These can be acquired through a first aid course, where the principles of saving a life can be learned. Equally important is the implementation of evacuation and rapid transport measures to the nearest health unit so that the injured person can receive medical assistance from the specialized personnel.

Practical Application 12.1.

Describe 2 situations of emergency in the pharmacy with elaboration of the medical assistance.

State of emergency and cause of emergence	Symptomes of state of emergency	First aid measures
E.g. *Medium severity anaphylactic shock after intramuscular benzylpenicillin administration*	*Palpitations, hypotension, sudden weakness, dizziness, visual disturbances, psychomotor agitation sensations regarding, fear of death, tremor, pallor, cold sticky sweating, loss of hearing.*	*To lay the person on the back, on a flat surface, with the lower limbs raised (20-30 cm).* *Removal of the tight clothing on the body and, if possible, cover the person with a blanket.* *Blockage of the affected area with s / c injections of epinephrine (0.1% - 0.2-0.3 ml).* *Epinephrine is recommended to be administered intravenously slowly and with extreme caution 0.1-0.5 mg (0.1-0.5 ml in the ampoule), diluted with 10 ml isotonic saline or* *Dexamethasone will be given intravenously at a dose of 24 mg.*

Practical Application 12.2.

Describe 3 medications used in state of emergency.

Medicaments used in state of emergency. Pharmacological Group	Mechanism of action and pharmacological effects	Dosage and administration mode	Indications	Contraindications and adverse reactions
E.g. Epinephrine Alpha and beta adrenomimetic	The therapeutic doses reduce the congestion and the edema of the mucous membranes (by vasoconstriction and the diminution of the capillary permeability), they stimulate the heart and they slightly increase the systolic pressure, they	In anaphylactic shock, intravenously slow and very cautious 0.1-0.5 mg (0.1-0.5 ml in ampoule), diluted with 10 ml isotonic saline; if not possible, inject 0.5-1 mg (1 / 2-1 ampoule) intramuscularly or administer 1 mg perlingually (20 drops of the solution for internal use or one ampoule). In cardiac syncope, intravenously slowly 0.5-	Allergic emergencies - anaphylactic shock, laryngeal angioedema; cardiac arrest (by ventricular asystole); access to asthma; surface capillary haemorrhages (in local application); is associated with	Contraindications. High blood pressure, myocardial disease, ischemic heart disease, tachycardia and ectopic arrhythmias, atherosclerosis, pulmonary cord, hyperthyroidism, pheochromocytoma, narrow-angle glaucoma, prostate adenoma with urinary retention, severe renal failure; caution in diabetics, in

	have bronchodilating action; locally it causes vasoconstriction and may stop capillary bleeding. The effects are due to direct sympathomimetic action (alpha- and beta-adrenergic stimulation).	1 mg (1 / 2-1 ampoule), possibly repeated after 1-15 minutes; if not possible, the same dose is injected into the heart cavity. In bronchial asthma, subcutaneously 0.3 mg (0.3 ml of ampoule), possibly repeated at 20 minutes (maximum 2-3 doses). In local applications, as hemostatic, solution 1/100 000-1 / 2 000; associated with local anesthetics, in 1 / 200,000-1 / 20,000 solution.	local vasodilatory anesthetics (procaine, lidocaine) to prolong their action and reduce their overall toxicity.	hypercalcemia and hypokalaemia. Side effects. Palpitations, tachycardia, ectopic arrhythmias, angina pains, anxiety, restlessness, weakness, dizziness, headache, limb paralysis, increased blood sugar. Intravenous injections are dangerous (extreme caution).

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Chapter 13.

INTERPRETATION OF LABORATORY ANALYSIS.

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The analysis of laboratory data by a pharmacist could guide the confused patient into all the data presented by a laboratory, as it is not yet decided to visit a doctor. From this point of view, the pharmacist being one of the most accessible persons with competences in the medical field could be an important help for the patient.

The student and later the pharmacist must possess sufficient knowledge to be able to appreciate any values if they are within the norm or are present deviations to increase or decrease.

The following are some tables with the most important and frequently used biochemical parameters of diagnostic relevance:

PARAMETERS OF HEMOLEUCOGRAM

The hemogram is a basic screening test, being one of the most frequently requested laboratory tests, often representing the first step in establishing the hematological status and the diagnosis of various hematological and non-hematological diseases. The quantification of the hematological parameters sometimes associated with the examination of the blood smear provides valuable information, further orienting itself to perform other specific tests.

Table 13.1.

Blood analysis

Blood analysis	Normal values	Increase	Decreases
Leukocytes	4500-l0.000/mm3	Infections, tumors, intoxication, leukemia	Viral and bacterial infections, parasites, collagenosis, intoxication
Leukocyte formula **Non-segmented neutrophils** **Segmented neutrophils**	 3-5% 54-62%		
Eosinophils	1-3%	Allergic diseases, parasites, Hodgkin disease, pneumopathies, after radiation	The onset of infectious diseases, poisoning, post-corticosteroids
Basophils	0-0,75%	Deficiency of proteins, some forms of leukemia and tumors, malaria	
Limphocytes	25-33%	TB at onset, scarlet fever, whooping cough, chronic lymphocytic leukemia	Serious infections, Hodgkin's disease, after corticosteroids
Monocytes	3-7%		Infectious mononucleosis, endocarditis, leukemia brucellosis, malaria
Erythrocytes **men** **woman** **children**	 4,6-6,2 mil/mm^3 4,2-5,2mil/mm^3 4,5-5,1 mil/nun^3	Poliglobulii	Anemia
Reticulocytes	0,2-2%	Hemolytic, post-hemorrhagic anemia, regeneration phase of anemia	Aplastic anemia
Platelets	150-350 mii/mm^3		Disseminated intravascular coagulation (DIC) purple thrombocytopenia
Fibrinogen	250-450 mg%	Acute rheumatic fever, pneumonia	Severe liver failure, leukemias, prostate cancer, pancreas
R **Men** **Woman**	 3-10 mm/1 oră 5-18 mm/2 ore 6-12 mm/1 oră 6-20 mm/2 ore	Infections, dysglobulinemia, evolutionary cancer, TB, infarction, septicemia, leptospirosis, lupus, pregnancy, menstruation	Hepatitis, polycythemia, allergic reactions. thalassemia, heart failure
matocrit **Men** **Woman** **Newborns** **Children**	 42-52% 37-48% 49-54% 35-49%	Hemoconcentrations	Hemodilutions, certain forms of anemia

Blood analysis	Normal values	Increase	Decreases
moglobin **Men** **Woman** **Newborns** **Children**	 13-18 g/dl 12-16 g/dl 16,5-19,5 g/dl 11,2-16,5 g/dl		Anemia
Coagulation time	5-15 min.	Hemophilia, Hiperfibrinogenemie, DIC	
Prothrombin time	12-14 sec.	Anticoagulant medication, deficiencies of synthesis or functioning of coagulation factors	Increased intake, absorption or increased use of vitamin K, mechanical jaundice, liver damage.
Howell time	50 sec.-1 min. 20 sec.	Hemophilia, hypofibrinogenemia, DIC., anticoagulant treatment	
Iron	50-150 µg/dl	Post-haemorrhagic, feriprive, avitaminosis, malignant tumors, absorption disorders	Biermer's anemia, hemolytic anemia and jaundice, hepatitis, hememosiderosis.

Table 13.2.

BLOOD BYOCHEMISTRY

Blood analysis	Normal values	Increase	Decreases
Alanine aminotransferase (ALT) SGPT	5-35 U/l	Viral hepatitis, myocardial infarction, cirrhosis, pulmonary and renal infarction, muscle necrosis, cholecithiasis, pancreatic carcinoma	
Aspartate aminotransferase (AST) SCOT	7-40 U/l	Myocardial infarction, viral hepatitis, cirrhosis, pulmonary and renal infarctions, muscular necrosis, cholecithiasis, pancreatic carcinoma	
Albumin	3,5-5,5 g/dl		Acute and chronic hepatitis, malnutrition, infectious diseases, nephrotic syndrome, gastro-enteropathy. alcoholism, cirrhosis
Alpha-fetoprotein	sub 10 Ul/ml	Liver cancer, testicular tumors	
Ammonia	11-35 umol/1	Metabolic, respiratory acidosis	Metabolic, Respiratory alkalosis, renal acidosis
Serum amylase	25-125 U/l	Acute pancreatitis, mumps	Diabetic coma
Lactic acid	4,5-19,8 mg/dl	Glycogenosis, epilepsy, heart attack, tumors, drug poisoning	Renal insufficiency
Uric acid	2,3-8,5 mg/dl	Gout, nephritis, leukemias	
Total fatty acids	190-420 mg/dl	Diabetes, hyperthyroidism, pheochromocytoma, obesity, glycogenosis, alcoholism, stress, pregnancy	
Non-esterified fatty acids	8-25 mg/dl		
Bicarbonate (HC03)	22-26 mEq/1	Alkalosis from intense vomiting	Acidoses from unbalanced diabetes, uremic kidney failure, diarrhea, pancreatic fistula
otal bilirubin	0,3-1,1 mg/dl		
direct	0,1-0,4 mg/dl	Mechanical jaundice through stones or tumors	
indirect	0,2-0,7 mg/dl	Jaundice by hemolysis: hepatitis, cirrhosis	
Calcium	4,5-5,5 mEq/1 (9-11 mg/dl)	Hypervitaminosis D, multiple myeloma, tumors or bone infections	Hypoparathyroidism, severe rickets, hypovitaminosis D, tetanus
Chlorine	96-106 mEq/l	Kidney disease	Sunburn, vomiting, diarrhea, chronic adrenal insufficiency.
Cholesterol **total** **esterified**	 150-200 mg/dl 68-76% din total	Diabetes, obesity, alcoholism, mixedem, nephrotic syndromes, jaundice	Cirrhosis, serious infectious diseases, pneumonia, malignant endocarditis, hyperthyroidism
Cholinesterase	2.25-7,0 Ul/1	Nephrosis, pancreatic cancer, obesity, diabetes	Forms of leukemia, subacute hepatitis, cirrhosis, liver metastases, lack of protein in the diet
Copper	70-155 ug/ml	Hepato-lenticular degeneration (Wilson's disease), acute or chronic infections	
Creatine fospho-kinase (CPK)	30-170 U/l	Myocardial infarction, muscular dystrophy and trauma, polymyositis, dermatomyositis, cerebral haemorrhage, sleeping poisoning.	
Creatinine	0,6-1,2 mg/dl	Kidney disease, gout, liver disease, myositis	

Blood analysis	Normal values	Increase	Decreases
Acid phosphatase	0,11-0,60 U/l	Prostate cancer	
Alkaline phosphatase	20-90 U/l	Paget's disease, hyperparathyroidism, cholestasis, rickets, osteomalacia, bone tumors, liver tumors	
Phospholipids	6-12 mg/dl	Biliary cirrhosis, mechanical jaundice, nephrotic syndrome, diabetes, hyperlipemia, hypercholesterolemia	
Inorganic phosphorus	2,6-4,5 mg/dl	Acromegaly, giganticism, kidney failure, hypervita-minosis D2, hypoparathyroidism.	Hyperparathyroidism, growth disorders
Gamma-Glutamyl transpeptidase (GGT)	1-60 U/l	Acute hepatitis, toxic hepatitis, antidepressant treatment, tumors, biliary cirrhosis	
Blood sugar	70-115 mg/dl	Different forms of diabetes, infections, carbon dioxide poisoning, tumors, strokes	Adrenal cortical insufficiency. Thyroid. pituitary, severe hepatic, after high doses of antidiabetics
HDL	30-80 mg/dl		Atherosclerosis, myocardial infarction
Lactat dehydrogenase (LDH)	100-190 U/l	Chronic hepatitis, cirrhosis, pancreatitis, pulmonary infarction, some anemias, malignancies	
Total lipids	450-850 mg/dl	Nephrotic syndrome, liver cirrhosis, mechanical jaundice, diabetes, acute pancreatitis, mixedem, hypercorticism, arteritis	
LDL	60-180 mg/dl	Atherosclerosis, myocardial infarction, inflammation	
Magnesium	1,5-2,5 mEq/ 11,8-3,0 mg/dl	Hyperthyroidism, kidney failure, cirrhosis	Rickets, mixedem, nephrosis, tetany
Potassium	3,5-5,0 mEq/1	Shock states, burns, bleeding, heart attack, malignant disease, hemolysis, nephritis	Diarrhea, vomiting, Cushing's disease, adrenal tumors, cortisone treatment
Total protein	6-8 g/dl	Hemoconcentrations, insufficient fluid intake, diarrhea, vomiting, cholera, unbalanced diabetes, myeloma	Hemodialysis, malnutrition, kidney disease, cirrhosis, shock, hemorrhage, chronic poisoning
Albumin	3,5-5 g/dl 52-68%		Lipoid necrosis, cirrhosis
Alpha l giulin	0,2-0,4 g/dl 2-5%	Myocardial infarction	
Alpha 2 globulin	0,5-0,9 g/dl 7-14%	Lipoid necrosis, acute joint rheumatism, TB, infectious hepatitis	
Beta globulin	0,6-1,1 g/dl 9-15%	Cirrhosis	
The globulin range	0,7-1,7 g/dl 11-21%	Collagenosis, hepatitis, cirrhosis, infections, jaundice	
Albumin/globulin ratio	1,2-1,5		
Sodium	136-145 mEq/1	Dehydration, heart failure, cortico-adrenal hyperfunction	Vomiting, diarrhea, adrenal insufficiency
Triglycerides	40-150 mg/dl	Pregnancy, essential hyperlipemia, atherosclerosis, hypothyroidism, nephrotic syndrome	Chronic infections, hyperthyroidism, some forms of cancer
Urea	21-43 mg/dl	Acute or chronic kidney disease, diabetes, fever	Liver disease

Table 13.3.

Hormonal determinations in the blood

Blood analysis	Normal values	Increase	Decreases
Aldosterone **orthostatism** **clinostatism**	 5-30 ng/dl 3-10 ng/dl	Conn syndrome, heart failure, cirrhosis, treatment with diuretics. laxatives	Addisson disease, virilism
Calcitonin **Men** **Woman**	 0-20 pg/ml 0-28 pg/ml	Spinal cancer, pheochromocytoma, carcinoid, bronchial tumors	
Catecholamines **adrenaline** **noradrenaline** **dopamine**	 0-140 pg/ml 70-1700 pg/ml 0-30 pg/ml	Pheochromocytoma, neuroblastoma	
Corticotrophin (ACTH)	6-76 pg/ml	Cushing's disease, bronchial, pancreatic, thymic tumors, hypercorticism, stress	Corticostrenal tumors, hypothalamo-pituitary insufficiency, corticosteroids

Blood analysis	Normal values	Increase	Decreases
Cortisol **8 o'clock** **16 o'clock** **22 o'clock**	 6-23 µg/dl 3-15 µg /dl 0-10 µg /dl	Cushing's disease, liver disease, stress	Addison's Disease, pituitary insufficiency
FSH (follicle stimulating hormone) **man** **woman** **postmenopausal**	 4-25 UI/1 4-30 UI/1 40-250 UI/1	Menopause, primary ovarian failure	Hypothalamo-pituitary insufficiency, anovulatory cycles, estrogen administration
GH (Growth Hormone)	0-10 ng/ml	Pituitary adenoma: acromegaly, gigantism	Pituitary insufficiency: dwarfism
Gonadotropins	under 15-20 UI/1	Hypophyseal hyperfunction, tumors and lesions of the central nervous system, gonadal failure, seminal tumors	Delayed puberty, pituitary infantilism, amenorrhea, mental anorexia
Insulin	5-25 µU/ml	Insulinoma	Unbalanced diabetes
LH (luteinizing hormone) **man** **premenopausal midl-** **postmenopausal cycle**	 6-18 UI/1 5-22 UI/1 3 times basal over 30 UI/1	Menopause, ovarian failure, testicular failure	Gonadial insufficiency hypothalamohypophysis, polycystic ovary.
Parathyroid hormone	10-60 pg/ml	Parathyroid adenoma, lung carcinoma, nephropathy	Tetany
Pprolactin **woman** **men**	 1-25 ng/ml 1-20 ng/ml	Pituitary adenoma, amenorrhea, galactorrhea, some contraceptive	After administration of bromergocriptine, thyroid hormones, B6
Testosterone **man** **woman** **pregnancy**	 275-875 ng/dl 23-75 ng/dl 38-190 ng/dl	Testicular cancer, virilism, early puberty	Prostate cancer, Turner syndrome
TSH (thyroid stimulating hormone)	0-7 µU/1	Primary thyroid insufficiency, thyroiditis, goiter by enzymatic defects	Hyperthyroidism, hypothalamo-pituitary insufficiency
Free thyroxine	1,0-2,1 ng/dl	Hyperthyroidism, overeating	Hypothyroidism, alcoholism, intoxication
T4 thyroxine	4,4-9,9 µg /dl		
Triiodothyronine T3	150-250 ng/dl		

Table 13.4.

Biochemical immunological determinations of blood

Blood analysis	Normal values	Increase	Decreases
Carcinoembryonic antigen	under 5 ng/ml		
Complement **C_3**	83-177 mg/dl 15-45 mg/dl	Acute infections, neoplastic diseases, acute hepatitis	Autoimmune diseases: disseminated lupus erythematosus, glomerulonephritis, hemolytic anemia, chronic hepatitis
IgA	60-333 mg/dl	Alcoholic cirrhosis, glomerulonephritis, liver necrosis, myeloma	Nephrotic syndromes, spinal cord aplasia
IgG	550-1.900 mg/dl	Liver cirrhosis, pyelonephritis, lupus, myeloma, autoimmune glomerulo-nephritis	
IgM	45-145 mg/dl	Acute hepatitis, biliary cirrhosis, pyelonephritis, parasitic diseases, lupus	

Urine analysis. Chemical composition of urine.

Components	Variation range of concentration / 24 hours
Anions	
Chloride	9-12 g
Total sulfur (in SO3)	2,5-3 g
Phosphate (in P2O5)	2-3 g
Cations	
Sodium	2,2-7,8 g
Potassium	2-3 g

Ammonium salts	0,4-1 g
Calcium	0,14-0,20 g
Magnezium	0,08-0,15 g
Organic components	
Urea	15-30g
Uric acid	0,4-0,8 g
Creatinine	1,5-2 g
Creatine	60-150 mg
Amino acids	1-3 g
Glucose	200 mg
Hint	4-5 mg
Ketone bodies	3-15 mg
Uroporfirine	10mg
Proteine	30-40 mg
Amylase	14-32 U.Wohlgemuth 100-2000 U/l

URINE BIOCHEMISTRY

Urine is a biological excretion fluid, with a complex chemical composition, which may undergo changes in certain pathological conditions. Complete analysis of urine includes the determination of physical (color, appearance, specific weight), chemical (pH, protein, glucose, ketone, hematopoietic, bilirubin, urobilinogen, leukocyte, nitrite) and microscopic examination of the sediment.

Urine biochemistry is determined by a semi-quantitative method, most often on an automatic analyzer, using urine strips. This type of test is fast and measures the elements in the urine that are significant for kidney, urinary, liver and metabolic dysfunctions. In case of a pathological change, there is a color change in the test area, which is compared with a predefined color scale. The color intensity allows a semi-quantitative evaluation of the result.

Table 13.6.

Urine analysis. Chemical composition of urine.

Parameter measured	Value	Decreases	Increase
Quantity 24 hours Adults and children over 14 years: Children betwee 14 years Children between 5 and 8 years Children between 3-5 years Children between 1-3 years Newborn babies:	1000-1600 ml 800-1400 ml 650-1000 ml 600-700 ml 500-600 ml 30-60 ml	Oliguria	Polyuria
Density	1,015 – 1,025	Excessive water intake, diabetes insipidus, glomerulonephritis (low density, low urine volume), chronic pyelonephritis (tubular alteration affects the ability of the kidney to concentrate urine).	Proteinuria, nephrosis, diabetes, excessive water loss (abundant sweating, fever, vomiting, diarrhea), surgical stress (increased ADH secretion), congestive heart failure, pregnancy toxemia.
pH	4,8 - 7,8	Highly acidic urine (pH <4.5) occurs in malignant processes (increased protein destruction), fever, abundant diarrhea, diabetic or metabolic acidosis. Chronic polyarticular rheumatism. Old diabetes. Decompensated kidney failure.	Increased values of urinary pH (alkaline urine) are found in: Respiratory alkalosis. Metabolic alkalosis. Abundant vomiting (different etiologies). Urinary tract infections (urethritis, cystitis, skin, pyelonephritis).
Leukocytes	Negative		Inflammatory disorders of the urinary tract: bacterial infections (cystitis, urethritis, acute or chronic pyelonephritis), viral or fungal infections,

Parameter measured	Value	Decreases	Increase
			parasitic infestations (shistosomiasis), glomerulopathies, analgesic-induced nephropathy, intoxication, urinary discharge disorders.
Protein (albumin)	<10mg/dL		Indicator of renal impairment. Proteinuria can be transient (without kidney injury) in infectious conditions, febrile conditions, heart failure, acute pulmonary edema; intermittent (mild proteinuria that disappears spontaneously during the night and manifests itself under stress or fatigue, digestion, posture - orthostatic proteinuria) or permanent (associated with renal injury) in glomerulonephritis, nephrotic syndrome, localized kidney disease, tumors, lithiasis, tuberculosis.
Nitrites	Negative		The presence of large amounts of leukocytes and nitrites in the urine signal a urinary infection caused by bacteria such as Escherichia coli, Enterobacter, Klebsiella, Citrobacter etc.
Glucose	undetectable (> 1000 mg/dL (should be tested serum glucose)		Glycosuria occurs specifically in diabetes; other conditions associated with glycosuria are: hyperthyroidism, acromegaly, Cushing's disease, liver and pancreatic diseases, CNS diseases (brain trauma, stroke), impaired tubular glucose uptake (Toni-Debre-Fanconi syndrome, advanced renal tubular disease), possible pregnancy latent diabetes (gestational diabetes).
Ketone bodies	Negative		Alteration of carbohydrate metabolism occurs, high fat is metabolized, restricted carbohydrate intake or high fat diet, acidosis states: starvation, anorexia, diet high in lipids, protein and low carbohydrate, diabetes (diabetic acidosis) , dyspeptic conditions (vomiting, prolonged diarrhea, especially in children), eclampsia, renal glycosuria, glycogenosis (von Gierke's disease), hyperthyroidism, fever, pregnancy, lactation. The presence of ketone bodies in the urine of a diabetic patient suggests that diabetes is not well controlled. Ketonuria in a child <2 years old is an alert signal.
Erythrocytes	Negative		Lithiasis, glomerulonephritis, renal, ureteral or bladder tumors, cystitis, pyelonephritis, prostate adenoma, papillary necrosis, renal infarction, trauma, polycystic kidney, benign familial or recurrent hematuria, etc. Less often, hematuria may be a sign of hemorrhagic diathesis: hemophilia, thrombocytopenia, anticoagulant treatment.
Bilirubin	Negative		Urinary bilirubin is an early sign of hepatocellular disease or intra- or extrahepatic biliary obstruction (it appears in the urine before other signs of liver dysfunction). Also, its presence or absence in the urine is used in the differential diagnosis of jaundice.
Urobilinogen	Negative		Urobilinogen is elevated under conditions associated with hemolytic jaundice and liver failure. In case of complete obstruction of the bile ducts, urobilinogen is absent in the urine because bilirubin is prevented from reaching the intestine to form it. Thus, the presence of bilirubin in the urine in the absence of urobilinogen suggests obstructive jaundice.

FECAL MICROSCOPIC EXAMINATION

The microscopic examination of the stool brings information about the digestion of foods, during their passage through the digestive tract. The activity of various digestive enzymes on food can be determined by examining the muscle fibers, lipids (neutral lipids - triglycerides, free fatty acids, fatty acid salts - soaps and cholesterol), starch and cellulose (semi-quantitative test). These elements are quite rare in persons with normal digestion, even after the 3-day trial. Their presence in large quantities demonstrates digestive, absorption or intestinal transit disorders.

The reference values

- undigested muscle fibers: absent;
- digested muscle fibers: rare (<10 fibers / hpf *);
- neutral fats (triglycerides): <50 globules / hpf;
- free fatty acids, soaps: <100 globules / hpf;
- starch, cellulose: rare (5-10 granules / 10-15 hpf).
- hpf = high power microscopic field (40x)

Interpretation of results

✓ The presence of partially digested or undigested muscle fibers pleads for a digestive disorder: biliary obstruction, exocrine pancreatic dysfunction (cystic fibrosis), gastric fistula, gastric hydrochloric acid secretion (the muscle tissue cannot be digested in the intestine and the acid will not digest connective tissue)

or accelerated gastrointestinal transit.

- ✓ Increased fatty acids in the feces (especially fatty acids and soaps) are associated with malabsorption syndrome caused by: celiac disease, sprue, Whipple disease, regional enteritis, Crohn's disease, cystic fibrosis, malnutrition atrophy. Also, increased fat in the feces (especially neutral fats) is associated with malignancy caused by biliary obstruction, pancreatic disease in which there is a deficit of lipase (cystic fibrosis, chronic pancreatitis, neoplasm, obstructive calculus), short bowel syndrome after surgical resection, by-pass or congenital anomalies. There was a correlation between the presence of muscle fibers and fat in the feces.
- ✓ The presence of a large amount of starch in the stool demonstrates the pancreatic insufficiency, but also accelerated intestinal transit. The presence of a large amount of cellulose is the consequence, most often, of an accelerated intestinal transit.

Limits and interferences

For muscle fibers: bismuth, mineral oils, magnesium compounds.

For neutral fats and free fatty acids:

- Increase: laxatives, especially mineral oils, suppositories, lubricants, dietary mayonnaise intake, high fiber diet (> 100g/day).
- Decrease: Metamucil, barium.
- Other factors that may influence the test: alcohol, potassium chloride, calcium carbonate, Neomycin, Kanamycin and other broad-spectrum antibiotics, bismuth.

For sugars:

- Increase: newborn.
- Decrease: bacterial fermentation (if the sample is not analyzed immediately upon receipt in the laboratory and is not refrigerated).

Practical application 13.1.		
Problem	**Values** (in norme)	**Values (in the respective diseases)**
. Indicate the limits of the number of red blood cells, the level of hemoglobin and hematocrit if the patient has the respective degree of anemia (eg, grade I, II, III anemia).	Er – _____mil/mm3 Hb – _____% Hematocrit - _____g/dl	
. Indicate the changes in the biochemical analysis of the blood in the respective liver disease (eg viral hepatitis, alcoholic hepatitis, liver failure, etc.).	ALT – _____U/l AST – _____U/l LDH – _____U/l Albumin – _____g/dL Total bilirubin _____ mg/dl Direct bilirubin _____ mg/dl Indirect bilirubin _____ mg/dl	
. Indicate the changes in the urine analysis in the respective	Density – _____	

uroexcretory disorder (eg pyelonephritis, glomerulonephritis, nephrolithiasis, renal failure, etc.).	pH – _____ Leukocytes – _____ Erythrocytes – _____ Proteins – _____	

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