1.11. MEDICINES FOR PARENTERAL APPLICATION

See the video-film "Preparation medicines for parenteral application in pharmaceutical conditions"

INTRODUCTION

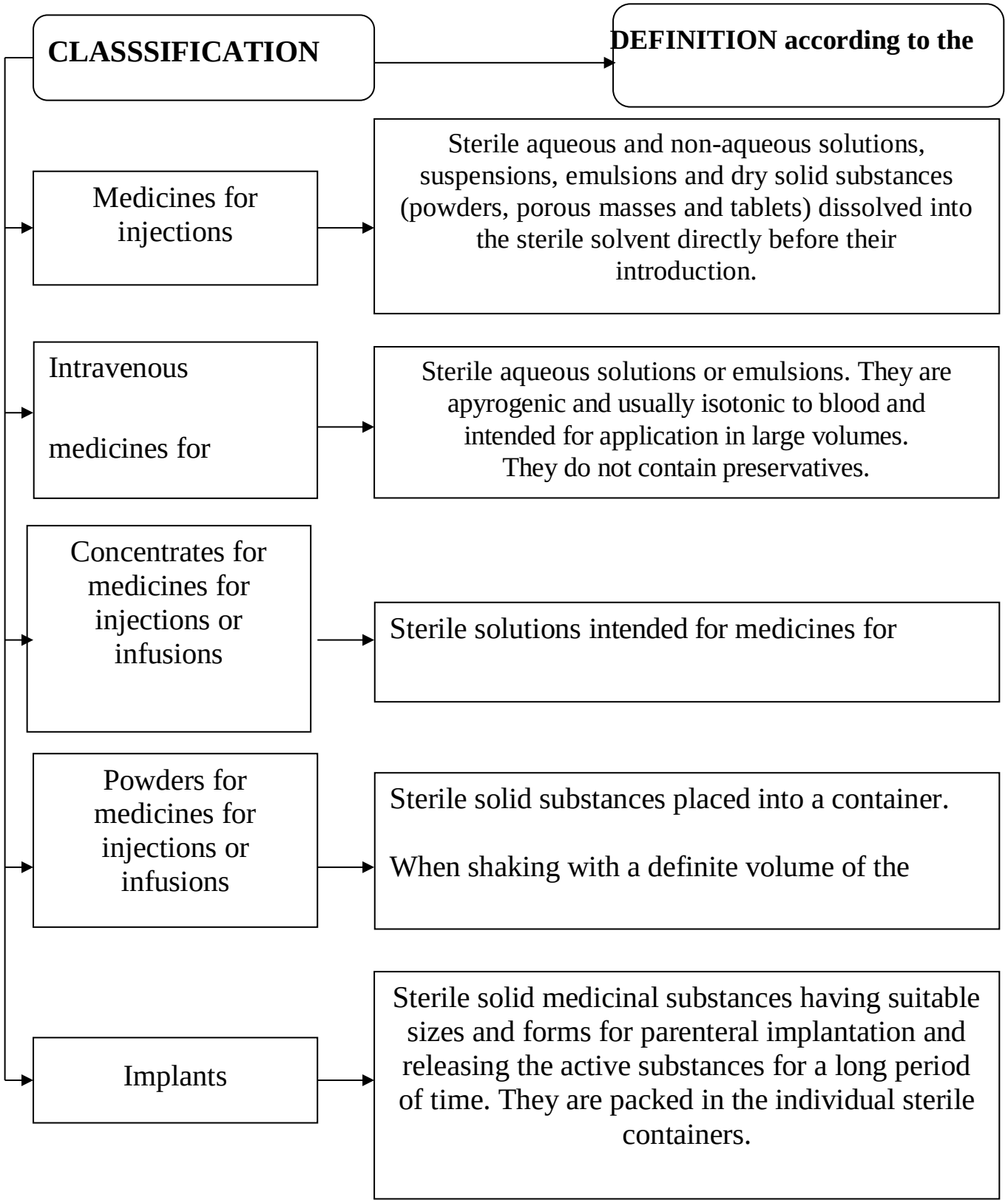
Nowadays a tendency to the production growth of medicines manufactured in sterile and aseptic conditions has been seen. Together with traditional medicines for injections and infusions, as well as eye drops pharmaceutical enterprises and institutions manufacture a large assortment of ophthalmic solutions for irrigations used in the ophthalmic microsurgery, liquid medicinal forms for children for internal and external application. This fact stipulates the necessity of the special requirements to organization of the technological processes of sterile medicines.

The research in developing and improving the formulation and the quality control of sterile medicines has been significantly extended. A number of methodical documents and NTD has been approved, they regulate the requirements to this group of medicines. The WHO at UNO has developed the unified international GMP requirements to the production of sterile medicines (they are observed by more than 80 countries of the world). New technologies, methods of control and equipment providing a higher quality of the sterile products have been introduced into the pharmacy practice.

1. CHARACTERISTICS OF PARENTERAL MEDICINES

PARENTERAL MEDICINES

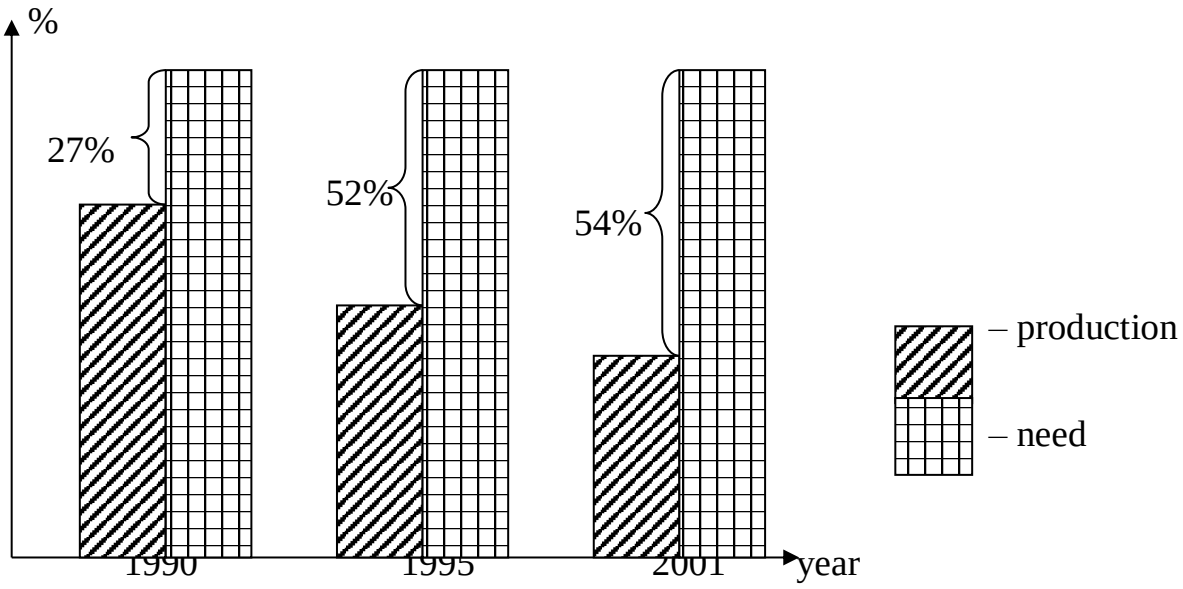
are sterile medicines for introduction by injections, infusions or implantations into a human or animal organism



2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

THE MARKET ANALYSIS OF PARENTERAL MEDICINES

- They occupy a significant place in the nomenclature of medicines.
- Germany has the most extensive assortment of medicines for infusions: 317 medicines of 38 pharmacotherapeutic groups.
- The pharmaceutical market of Ukraine presents 36 medicines of 16 pharmacotherapeutic groups. 25 of them are the medicines of the firms of Germany, Britain, Sweden, India, Poland, France, Japan, etc.
- The number of domestic medicines for infusions is only 9 of 7 pharmacotherapeutic groups.
- The difference between production and need in infusion solutions in Ukraine in 1990 was a 27 %, in 1995 – 52 % and in 2001 – 54 %.



2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

ANALYSIS OF THE NOMENCLATURE FOR PARENTERAL MEDICINES

Country, firm manufacturer	**The name of medicines**
Germany: **Braun Melsungen**	Metronidazole solution; aminoacid solutions: aminoplasmal, nephroplasmal, glucoplasmal, etc.; saline solutions: osmofundin, sterofundin, sodium chloride; plasma-substituting and detoxication solutions: oncovertin (dextran 40), helofusin, rehemaxel, plasmagel, Rheoges 4, Hemoges 6% and 10%, solutions of glucose and xylith with electrolytes, etc.
Fresenius AG	All groups of medicines for infusions.
Bayer	Infusion medicines for treating cardiovascular diseases: adalat (niphedipin), nimotop (nimodipin); antibacterial medicines of fluroquinolone group, etc.
Britain Glaxo Wellcome	Antiviral: zovirax (acyclovir), retrovir (zidovudin); antibacterial cephalosporine antibiotics: zinafer (sodium cefuroxim).
Sweden **Kabi Pharmacia**	Aminoacid medicines: vamine, vaminolac, oil intralipid emulsion.
USA Baxter, Abbott Laboratories, Pharmacia & Upjohn	Medicines with different direction of the action.
Japan	Medicines on the basis of aminoacids: moriamine, oil venolipid emulsion, plasma-substituting medicine on the basis of oxyethyl starch, 6 H.E.S.
Ukraine	Solutions of sodium chloride, glucose, dextran, «Trisol», «Reopolyglukin», etc.

2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

ANALYSIS OF THE NOMENCLATURE FOR PARENTERAL MEDICINES

Inter-hospital chemist's shops of Kharkov produce **20 names** of parenteral medicines:

The name of a pharmacy institution	**The name of medicines**
Kievsky district Chemist's shops №№ 288, 313, 314, 328, 336, 348	Solution of sodium chloride 0.9%, 10% Solution of novocain 0.25%, 0.5%, 1%, 2% Ringer solution Ringer-Lock solution Solution of amonicapronic acid 5% Solution of calcium chloride 5%, 10% Solution of glucose 5%, 10%, 20% Solution of trimecain 0.25%, 1% Solution of furacillin 0.02% Solution of sodium hydrocarbonate 4% Solution of potassium chloride 0.25%, 7.5% Solution of potassium iodide 3% Solution of etacridin 0.1% Solution of dimedrol 1% Solution of analgin 25%, 50% Solution of nicotinic acid 1% Solution of ascorbinic acid 5% Solution of sodium thiosulphate 30% Filips solution
Dzerzhinsky district Chemist's shops №№ 271, 315, 320, 329, hospital (Kultura str.)	
Moskovsky district Chemist's shops №№ 38, 307, 350	
Kominternovsky district Chemist's shops №№ 336, 348	
Leninsky district Chemist's shops №№ 321, 337	
Octyabrsky district Chemist's shop № 26	
Chervonozavodsky district Chemist's shop № 323	

- Extemporal medicines occupy their own niche, and manufactured medicinal forms could not have such place.
- A special care should be given to the pharmacy production: it should be up-to-date, rational, profitable and it should meet the international standards.

2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

PROVIDING THE NEED IN PARENTERAL MEDICINES

- **The need** in infusion medicines in Ukraine **is provided due to:**

- *industrial production of domestic medicines for infusions;*
- *medicines of the foreign manufacture;*
- *extemporal production in inter-hospital chemist's shops –30-40% of the total prescriptions.*

- **The leading enterprises of the branch** – «Stirolpharm» is the first in Ukraine and in former USSR's republics to cope with the production of medicines according to GMP regulations.

- The project of manufacturing liquid sterile medicines was realized by the American company «International Trade Clab. Inc.». The general cost of the project is 9.98 mln. US dollars.

- The assortment of medicines manufactured by «Stirolpharm» company is more than 10 names of different pharmacotherapeutic groups applied in the extreme medicine and ophthalmology.

2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

THE CHARACTERISTICS OF THE INJECTION WAY OF DRUG ADMINISTRATION

- The administration of medicines is performed by a syringe and a needle disturbing the integrity of the skin.
- For the first time the subcutaneous injection of medicines was made by Lazarev in 1851.
- A modern syringe was suggested by Pravats in 1852.

TYPES OF INJECTIONS:

- ✓ intracutaneous– injectiones intracutaneae;
- ✓ subcutaneous – injectiones subcutaneae;
- ✓ intramuscular – injectiones intramusculares;
- ✓ intravenous – injectiones intravenosae;
- ✓ intra-arterial – injectiones intraarteriales;
- ✓ intracranial – injectiones subarachnoidales;
- ✓ cerebrospinal – injectiones cerebrospinales, etc.

THE ADVANTAGES of the injection way of drug administration:

- The completeness of absorption and rapidity of action of the medicines introduced.
- Medicines are introduced without coming to the gastrointestinal tract and liver, where they can change or decomposed under the influence of enzymes.
- Discomfort relating to the unpleasant odor and taste of medicines is completely excluded.
- The possibility of exact dosing of medicines.
- The possibility of the localization of the drug action.
- The possibility of introducing the medicine to the unconscious patient.
- The possibility of the blood replenishment with the necessary volume of liquid after its considerable losses.

2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

THE DRAWBACKS of the injection way of drug administration:

- A serious danger of bringing infections into the organism appears.
- A danger of embolism appears (death is possible in embolism of vessels feeding the brain).
- Both physical and mental traumas are caused to a patient.
- The necessity of participation of the medical staff.
- Intravenous or intra-arterial introduction of great amounts of medicines can cause changes in blood pressure, pH medium, etc.

✓ At present the **METHOD OF INJECTION WITHOUT A NEEDLE** is used**:** the solution is introduced under the pressure into subcutaneous cellular tissues with the help of a special injector without disturbing the skin integrity.

THE ADVANTAGES of administering medicines by injections:

- Injections are painless.
- An effect comes rapidly.
- The required dose is decreased.
- It is impossible to transfer «syringe infections».
- The injector's sterilization is more seldom.
- The number of injections made in the unit of time (to 1000 per hour) increases.

2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

REQUIREMENTS TO PARENTERAL MEDICINES ACCORDING TO THE STATE PHARMACOPOEIA OF UKRAINE:

- Sterility;
- Stability;
- Apyrogenicity;
- Absence of particulate matters.

Requirements to some solutions:

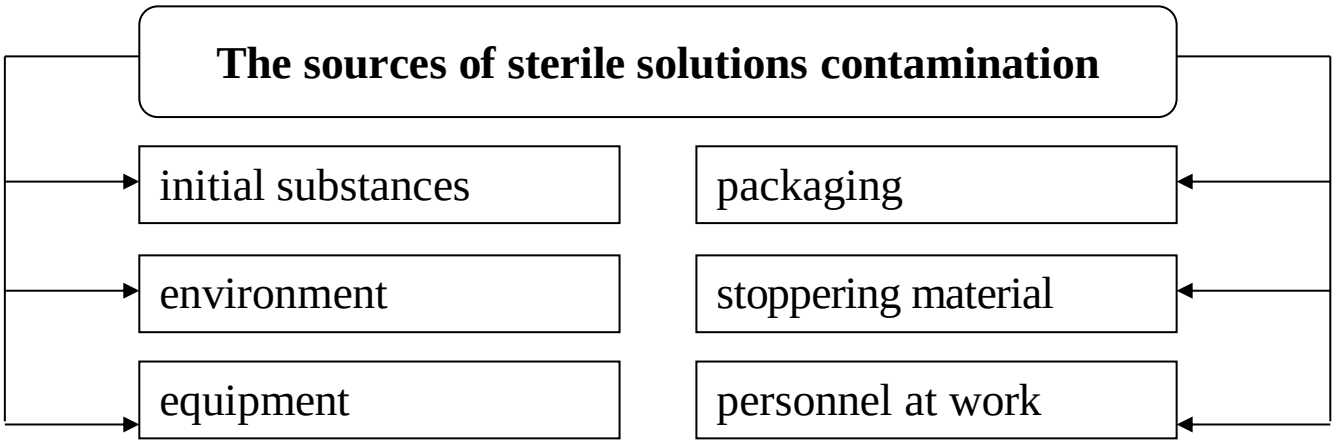
- Isotonicity;
- Osmolarity (osmolality);
- Isohydricity;
- Isoionicity.

- ✓ **Solutions for injections** should be transparent.
- ✓ **Emulsions for injections** should not have signs of stratification.
- ✓ **Suspensions for injections** should disperse rapidly when shaking.
- ✓ **Liquid parenteral medicines are checked by the following parameters of quality:** description, authenticity, transparency, color, pH, relating admixtures, extracted volume, sterility, pyrogens or bacterial endotoxins, abnormal toxicity, mechanical inclusions, assay.

2. MODERN STATE OF MANUFACTURING PARENTERAL MEDICINES

PREPARATION OF PARENTERAL MEDICINES

➢ They are prepared in aseptic conditions using materials and methods that provide sterility, prevent contamination of medicines and growth of microorganisms in them.



1. Asepsis is definite conditions of work, the complex of organizational measures that allow to prevent medicines from microorganisms as much as possible.

✓ **Aseptic conditions of preparing parenteral medicines include:**

- ♦ Requirements to the premises;
- ♦ Requirements to medicinal and auxiliary substances;
- ♦ Requirements to the manufacturing, personnel;
- ♦ Requirements to solvents;
- ♦ Requirements to stoppering material;
- ♦ Requirements to organization and performance of technological processes (dissolution, stabilization, filtration, sterilization, packing, labeling).

3. ORGANIZATION OF WORK IN THE ASEPTIC CONDITIONS

It is regulated by:

✓ The order of the Ukrainian Ministry of Health № 139 from 14.06.93 «About ratification of instruction on sanitary and anti-epidemic measures at the chemist's».

✓ The article at the State Pharmacopoeia of Ukraine «preparative methods for sterile products».

Requirements to the premises: The manufacture of medicines in the aseptic conditions is carried out in «pure» premises, where air purity by microbial particles and mechanical inclusions is regulated.

Aseptic block should consist at least three rooms:

1. *Pre-aseptic* – for preparing the personnel to work.
2. *Aseptic* – for preparing medicinal forms.
3. *Apparatus* – for sterilization, obtaining water for injections.

Requirements to medicinal and auxiliary substances:

Medicinal substances use qualifications «ch. p.» - chemically pure, «p. f. a.» - pure for analysis or «suitable for injections» and meet the requirements of the normative and technical documentation.

Auxiliary substances (stabilizers, preservatives, etc.), which are permitted to medical application and met the requirements of the normative and technical documentation.

Additional material (cotton, gauze, oil-paper, filters, etc.) are used sterile. It can be stored closed in jars with in-ground stoppers not more 3 days. The opened materials should be used within 24 hours.

3. ORGANIZATION OF WORK IN THE ASEPTIC CONDITIONS

THE LIST OF MATERIALS
USED WHEN PREPARING PARENTERAL MEDICINES

№ п/п	The name of the material	Qualification	Normative and technical documentation
1.	Medical gauze	hygroscopic	HOST 9412-77
2.	Medical cotton	hygroscopic	HOST 5556-81
3.	Filter paper		HOST 12026-76
4.	Indicator paper RIFAN		
5.	Cotton fabrics of coarse calico		HOST 116-80-76
6.	Cotton bandage	filtered	HOST 332-69
7.	Aluminium caps	K-3K-2 type, etc.	OST 64-009-87
8.	Rubber corks	52-369/1, etc. indicated in the order of the Ukrainian Ministry of Health № 139 from 14.06.93	TUU 6-00152253.014-96
9.	Parchment paper		HOST 1341-84
10.	Glass vials for blood and blood substituents	NS-2	HOST 10782-85
11.	Glassware for measuring, glassware for preparing solutions, etc.	corresponding to HOST	

3. ORGANIZATION OF WORK IN THE ASEPTIC CONDITIONS

REQUIREMENTS TO THE MANUFACTURING EQUIPMENT

The application of the small mechanization means while preparing solutions for injections is permitted if there is the possibility of their disinfection or sterilization.

N	THE LIST OF EQUIPMENT
1.	Aquadistillers AEV-10, (A-10), AEVS-25, AEVS-60, Khirana, etc. Collectors of water for injections
2.	Measuring mixer for preparing solutions for injections or other containers
3.	Mixers for preparing solutions (desktop and floor types) MI-2
4.	Apparatus of the direct type for filtering solutions
5.	Filter funnels with glass filters, glass funnels or separated filter funnels F-30
6.	Surgical electric suction pump. Water-suction pump
7.	A device for pumping solutions for injections DPS-3
8.	A device for controlling solutions for injections DC-2
9.	A device for pressing out caps on vials or a device for rolling vials
10.	Vapor medical sterilizers, etc.
11.	Balance, pH-meter, ionomers, etc.

♦ When preparing parenteral medicines at the chemist's shops home and foreign equipment providing the proper quality of solutions can be used.

4. SOLVENTS

➢ *Water for injections*, *fatty oils*, *ethyl oleate*, as well as *complex solvents* are used while preparing parenteral medicines.

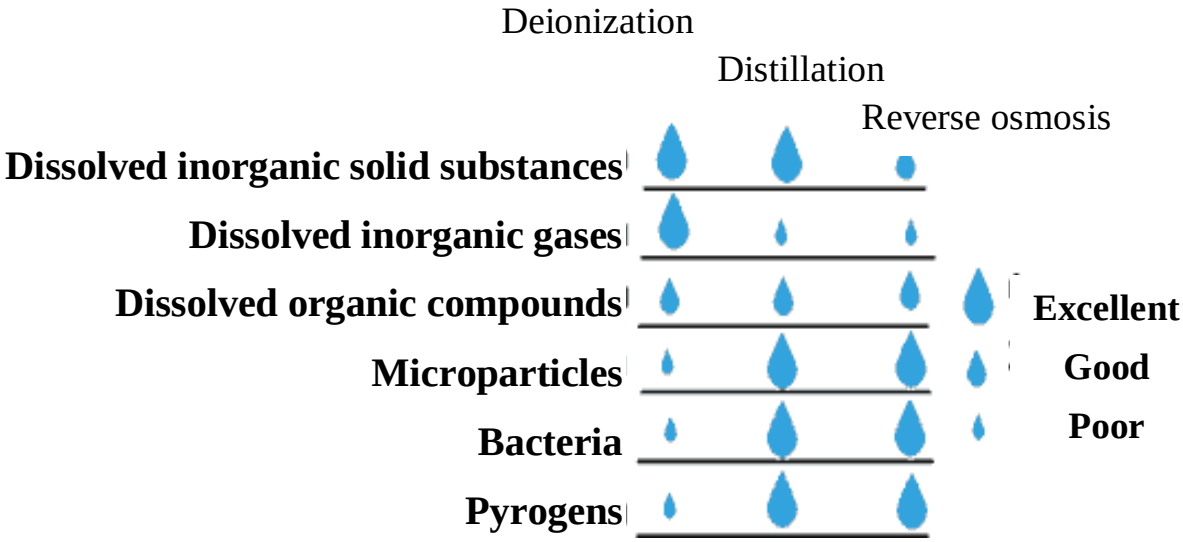
➢ ***Water for injections*** should meet the requirements to «Water for injections».

➢ Water for injections can be obtained by distillation of potable water in the aseptic conditions.

Types of water purification:

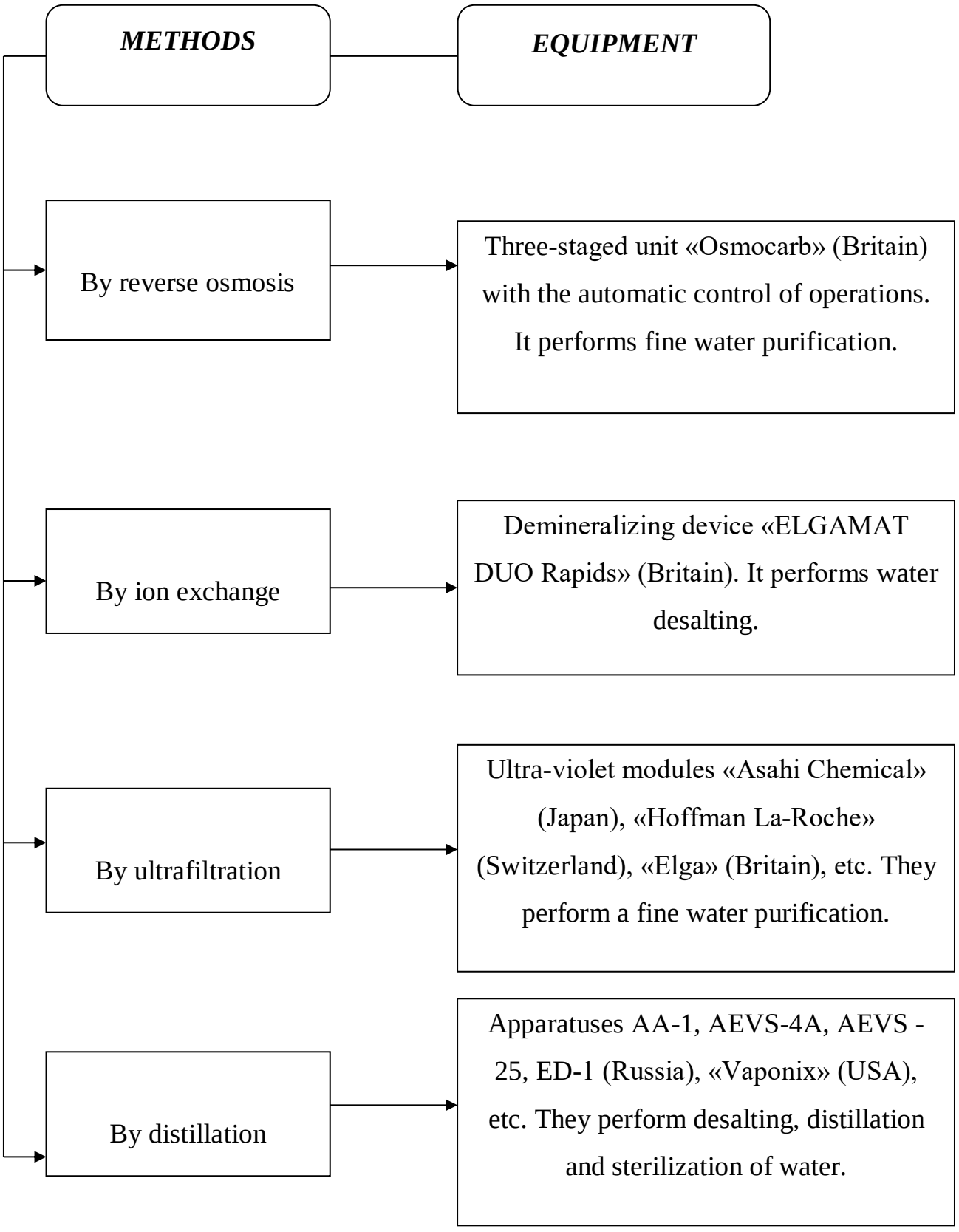
- distillation;
- reverse osmosis;
- deionization;
- ultrafiltration;
- sorption by activated carbon.

Efficiency of various types of water purification
in order to remove contaminants

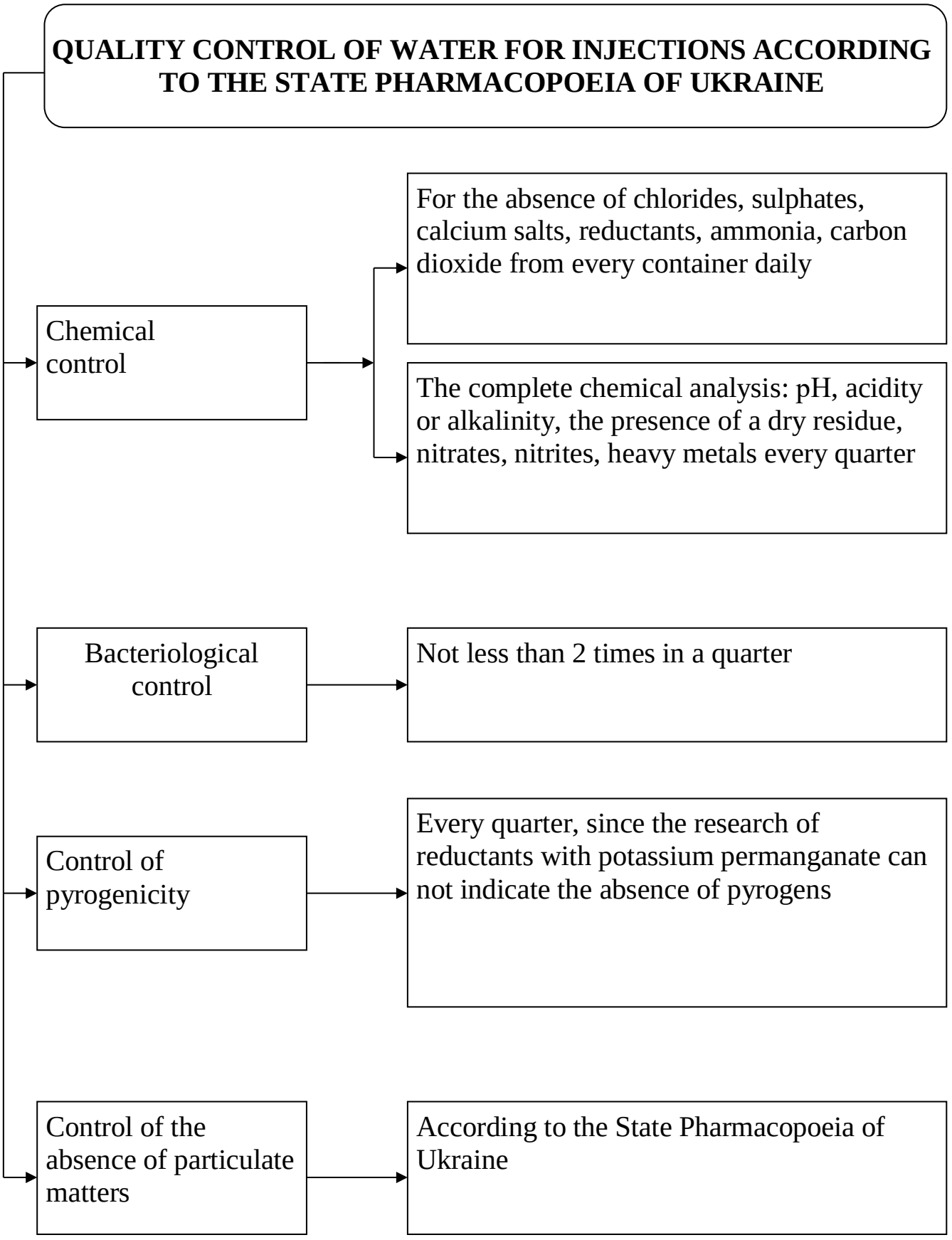


4. SOLVENTS

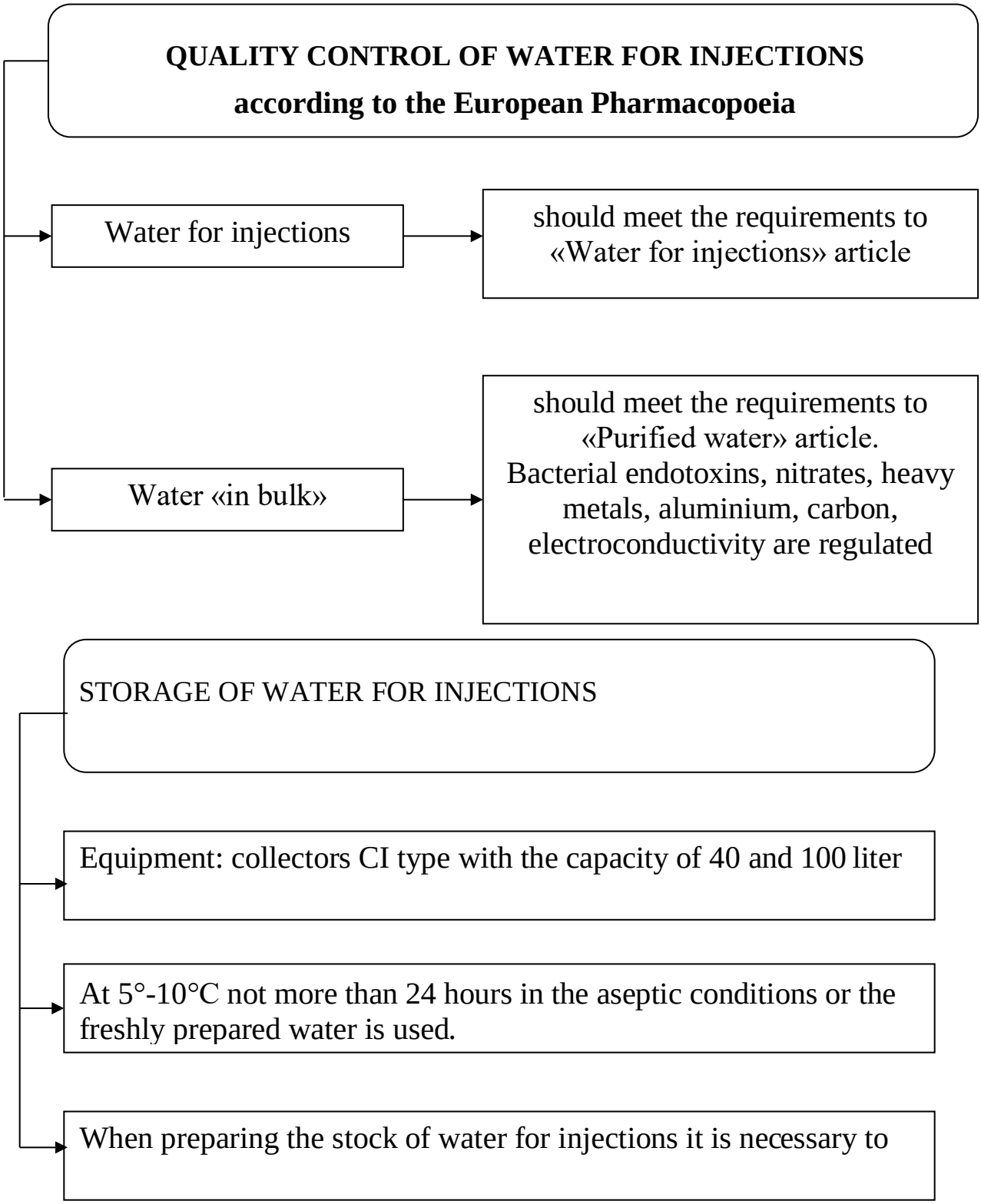
EQUIPMENT
FOR OBTAINING WATER FOR INJECTIONS



4. SOLVENTS


QUALITY CONTROL OF WATER FOR INJECTIONS ACCORDING TO THE STATE PHARMACOPOEIA OF UKRAINE
Chemical control
For the absence of chlorides, sulphates, calcium salts, reductants, ammonia, carbon dioxide from every container daily
The complete chemical analysis: pH, acidity or alkalinity, the presence of a dry residue, nitrates, nitrites, heavy metals every quarter
Bacteriological control
Not less than 2 times in a quarter
Control of pyrogenicity
Every quarter, since the research of reductants with potassium permanganate can not indicate the absence of pyrogens
Control of the absence of particulate matters
According to the State Pharmacopoeia of Ukraine

4. SOLVENTS


QUALITY CONTROL OF WATER FOR INJECTIONS
according to the European Pharmacopoeia
Water for injections
should meet the requirements to «Water for injections» article
Water «in bulk»
should meet the requirements to «Purified water» article. Bacterial endotoxins, nitrates, heavy metals, aluminium, carbon, electroconductivity are regulated
STORAGE OF WATER FOR INJECTIONS
Equipment: collectors CI type with the capacity of 40 and 100 liter
At 5°-10°C not more than 24 hours in the aseptic conditions or the freshly prepared water is used.
When preparing the stock of water for injections it is necessary to

5. CHARACTERISTICS OF PYROGENIC SUBSTANCES

Pyrogenic substances (from Greek *pyr* – fire, and Latin *generatio* - birth) are the products of the vital activity and decay of microorganisms, toxins, perished microbial cells.

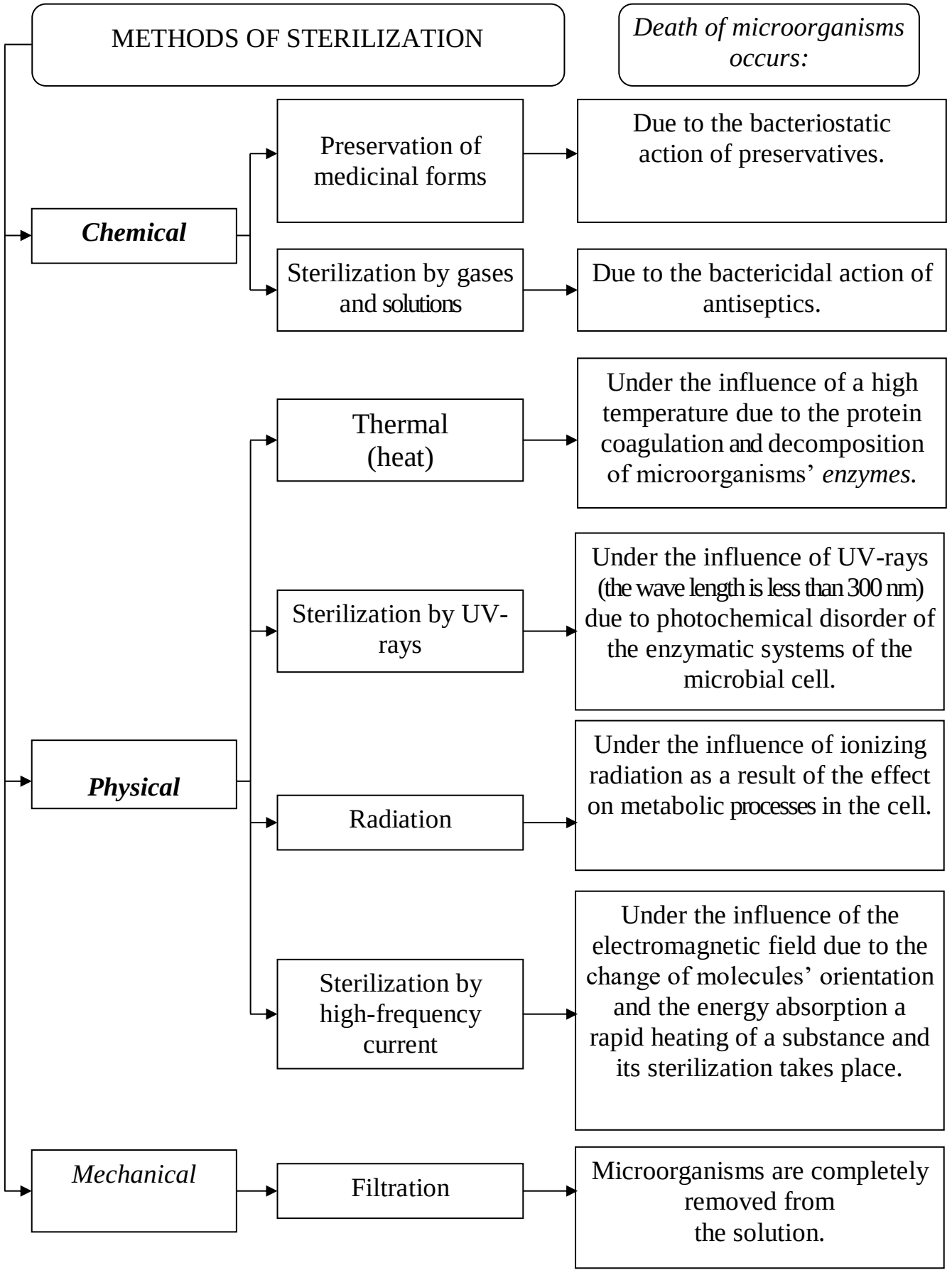
By the chemical composition: they are highly molecular compounds with a great molecular weight, have the liposaccharidic or lipopeptidic origin.

Properties: thermostable; non-volatile; are not distilled with water vapour → The thermal sterilization does not remove pyrogenic substances from water and solutions.

When entering into the organism: they cause allergic reactions, temperature increase, fever, cyanosis, asphyxia, up to anaphylactic shock and death → Toxicity is explained by the presence of phosphate groups in them.

6. STERILIZATION

➢ This is the process of complete destruction of microorganisms and their spores in medicinal substances, medicinal forms, vessels and glassware, auxiliary materials, instruments and apparatuses.



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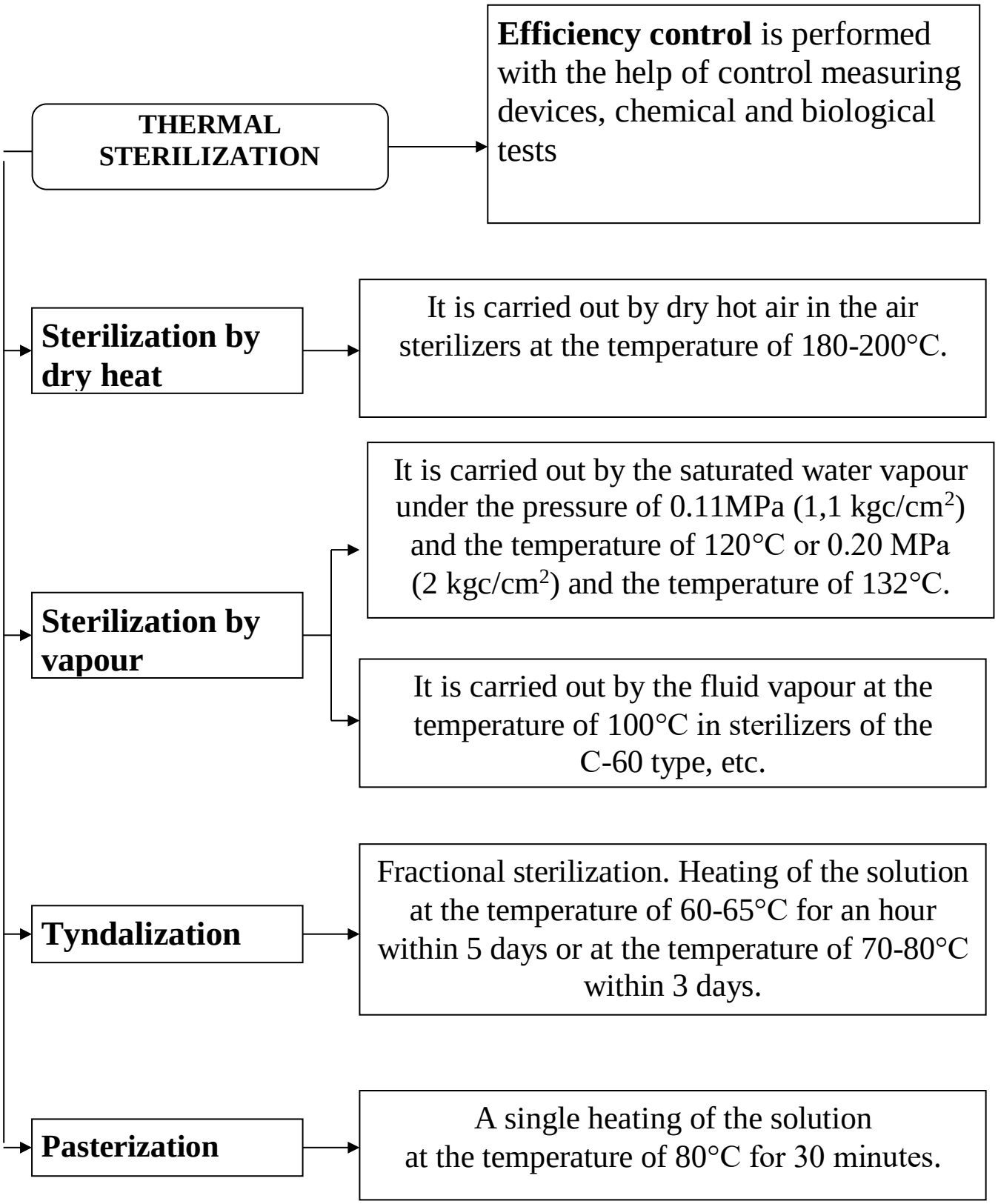

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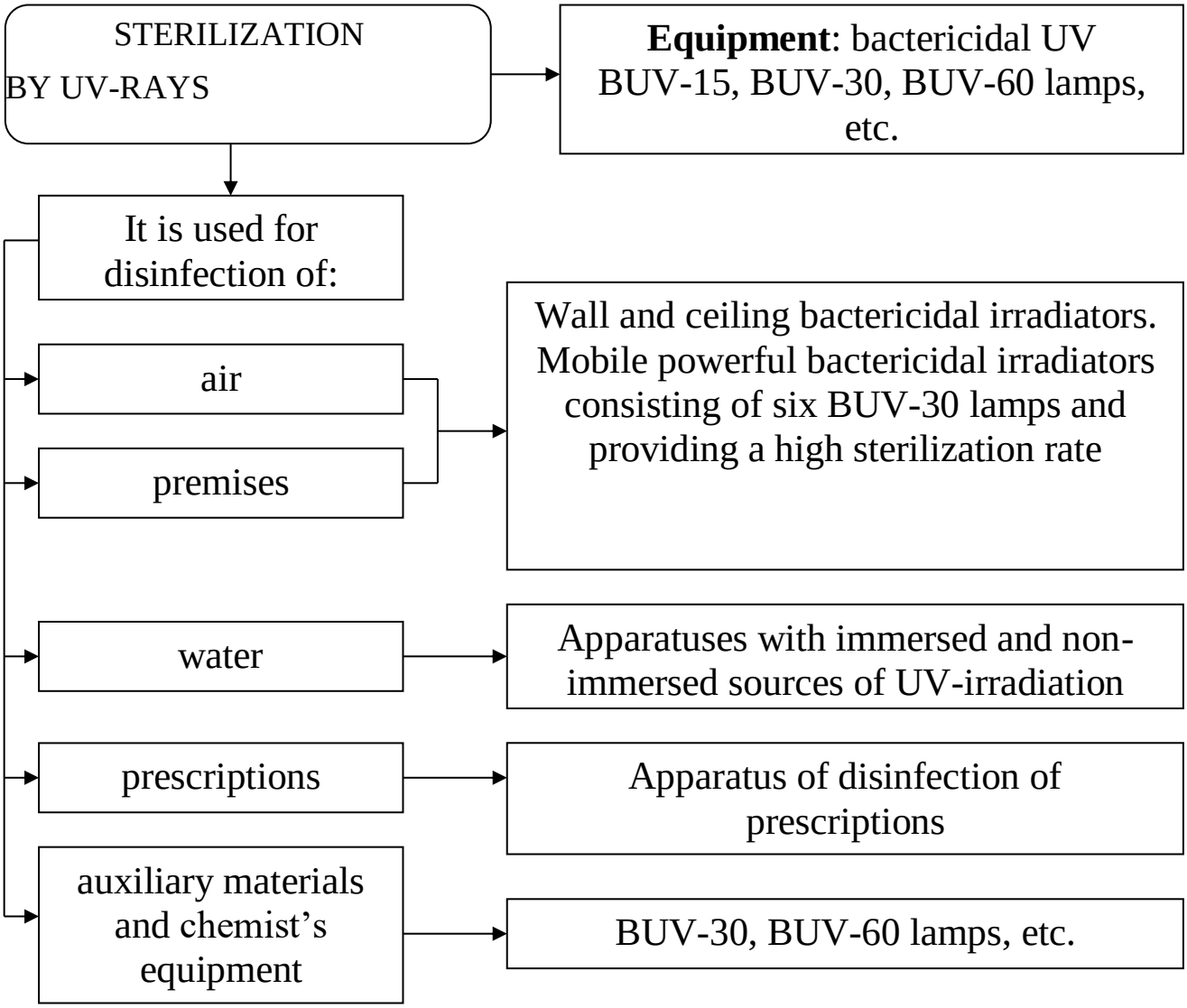
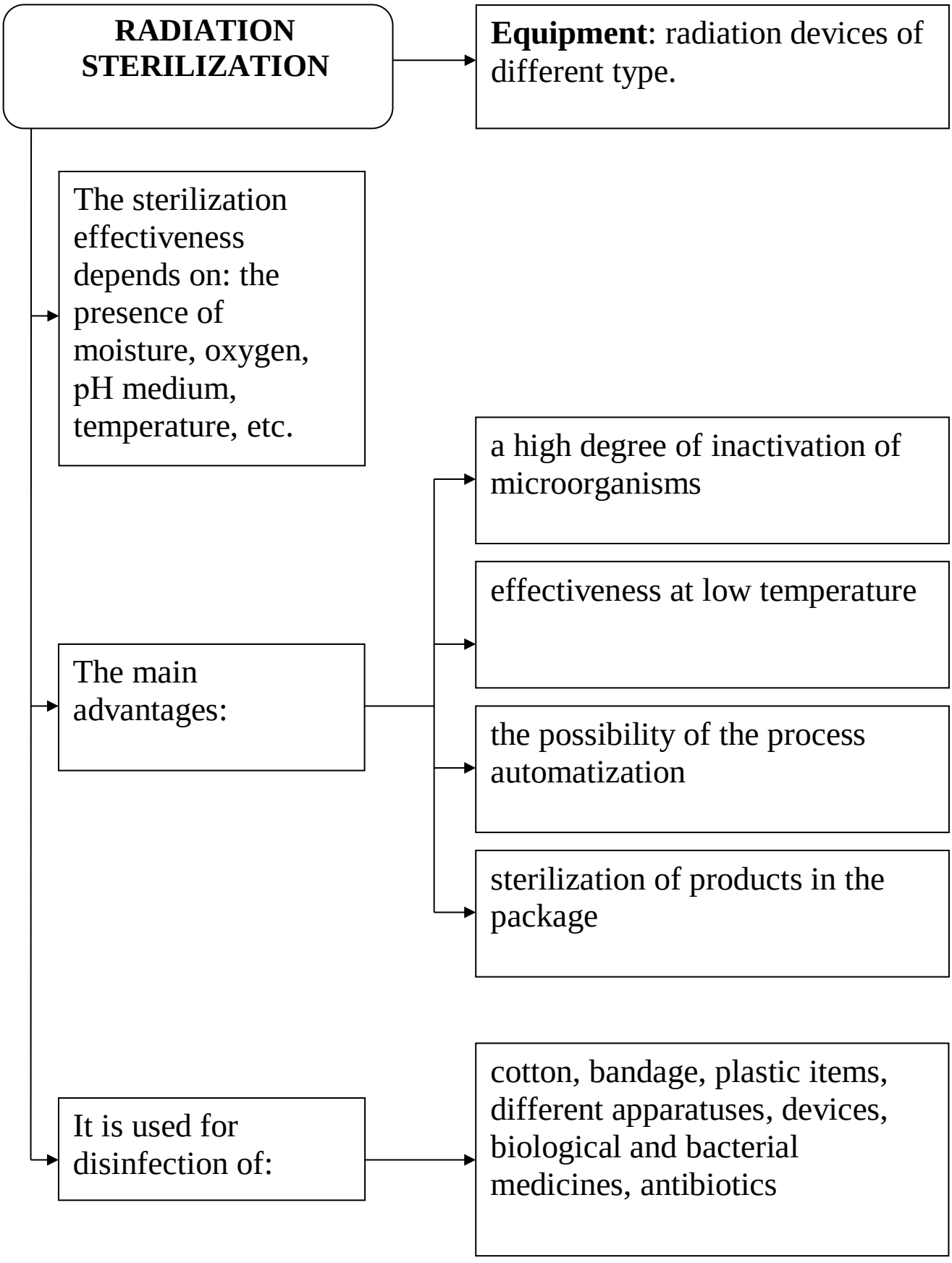


While sterilizing with the help of UV-irradiation one should observe the following rules:

- It is categorically forbidden to look at the lamp that is turned on as a burn of the eye conjunctiva and the skin can occur.
- When preparing medicines in the UV-irradiation area it is necessary to protect hands with 2% solution or 2% ointment of novocaine or paraaminobenzoic acid.
- It is necessary to air the premise in order to remove nitrogen oxides and ozone formed.

6. STERILIZATION



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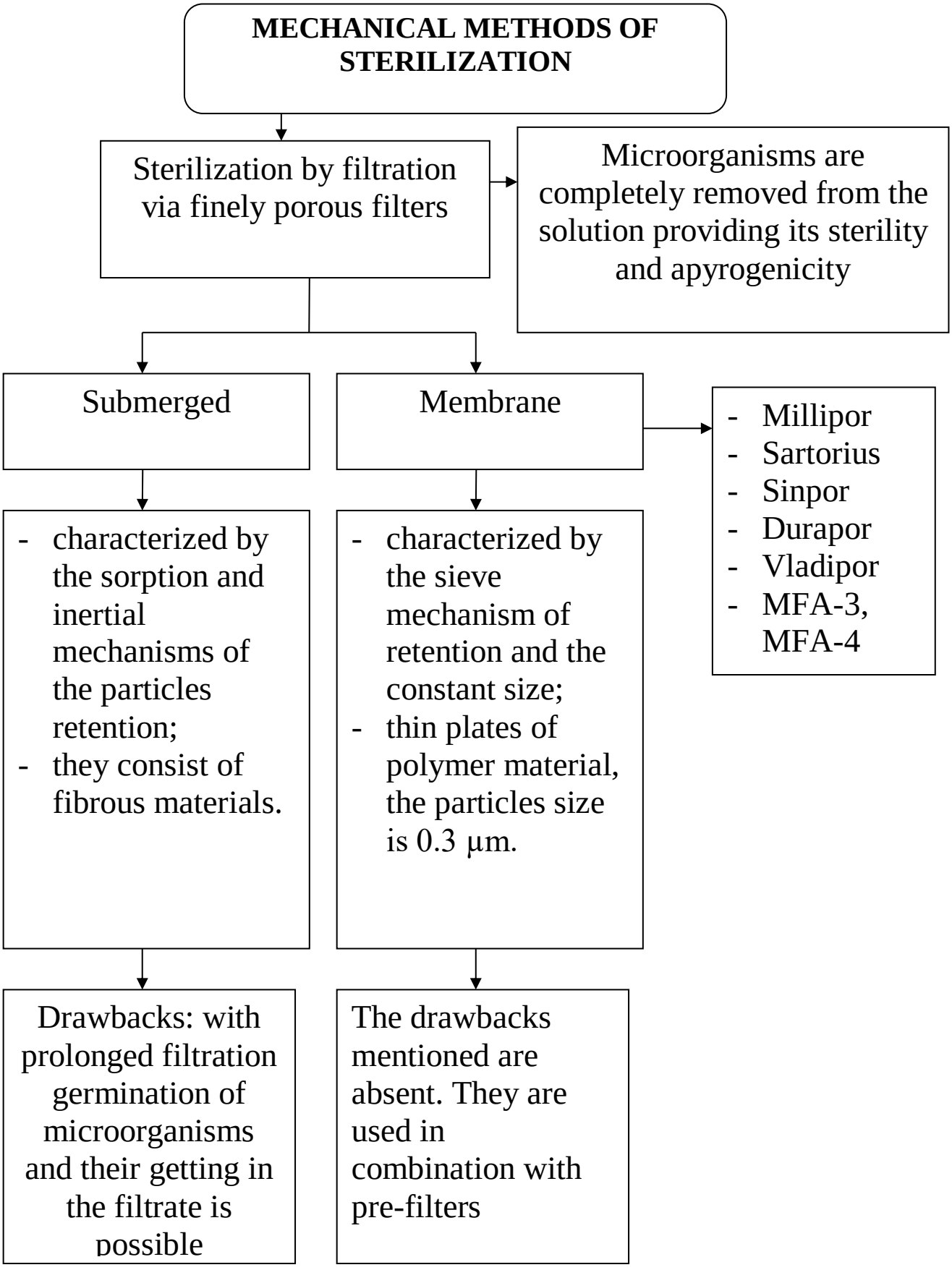
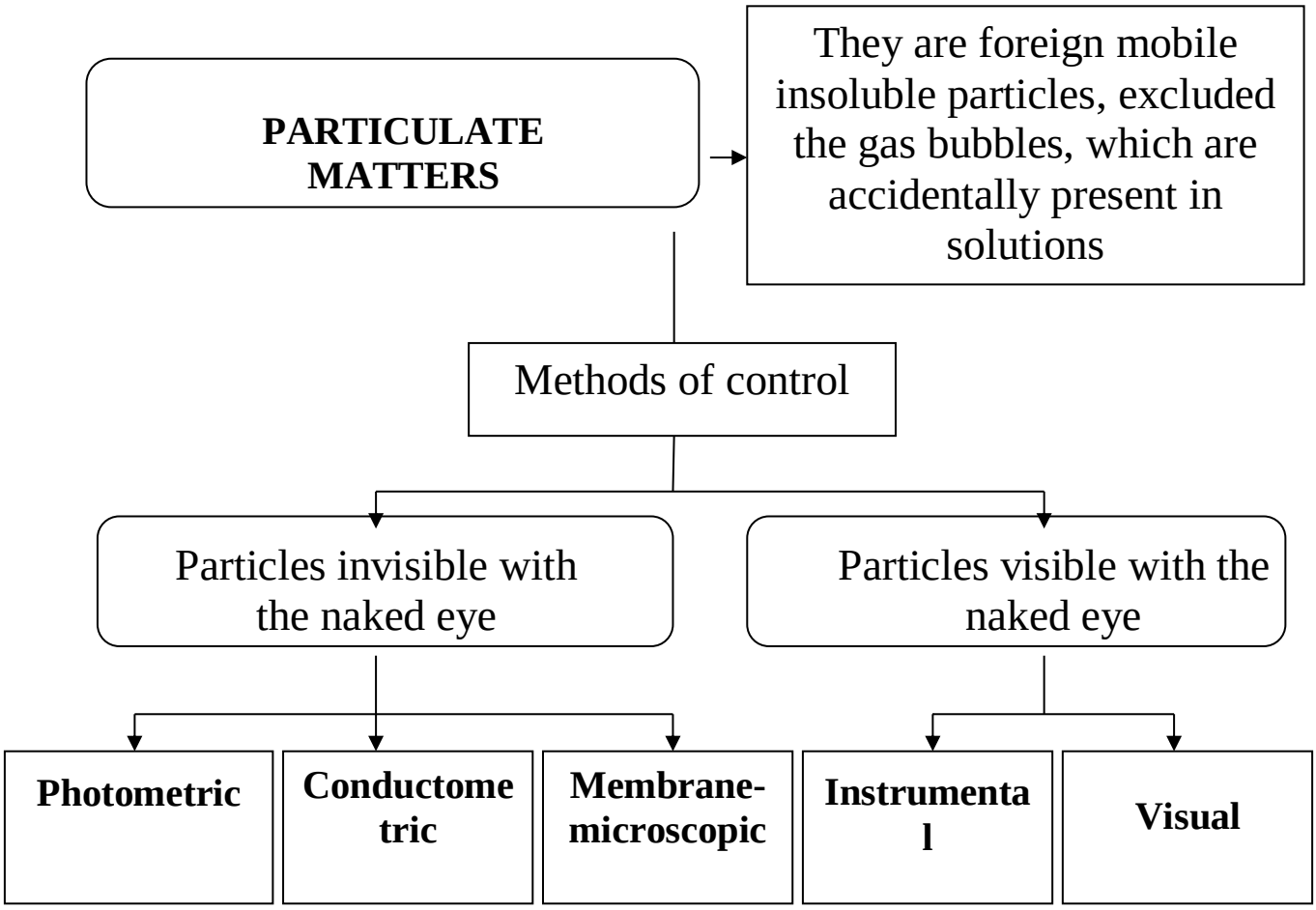


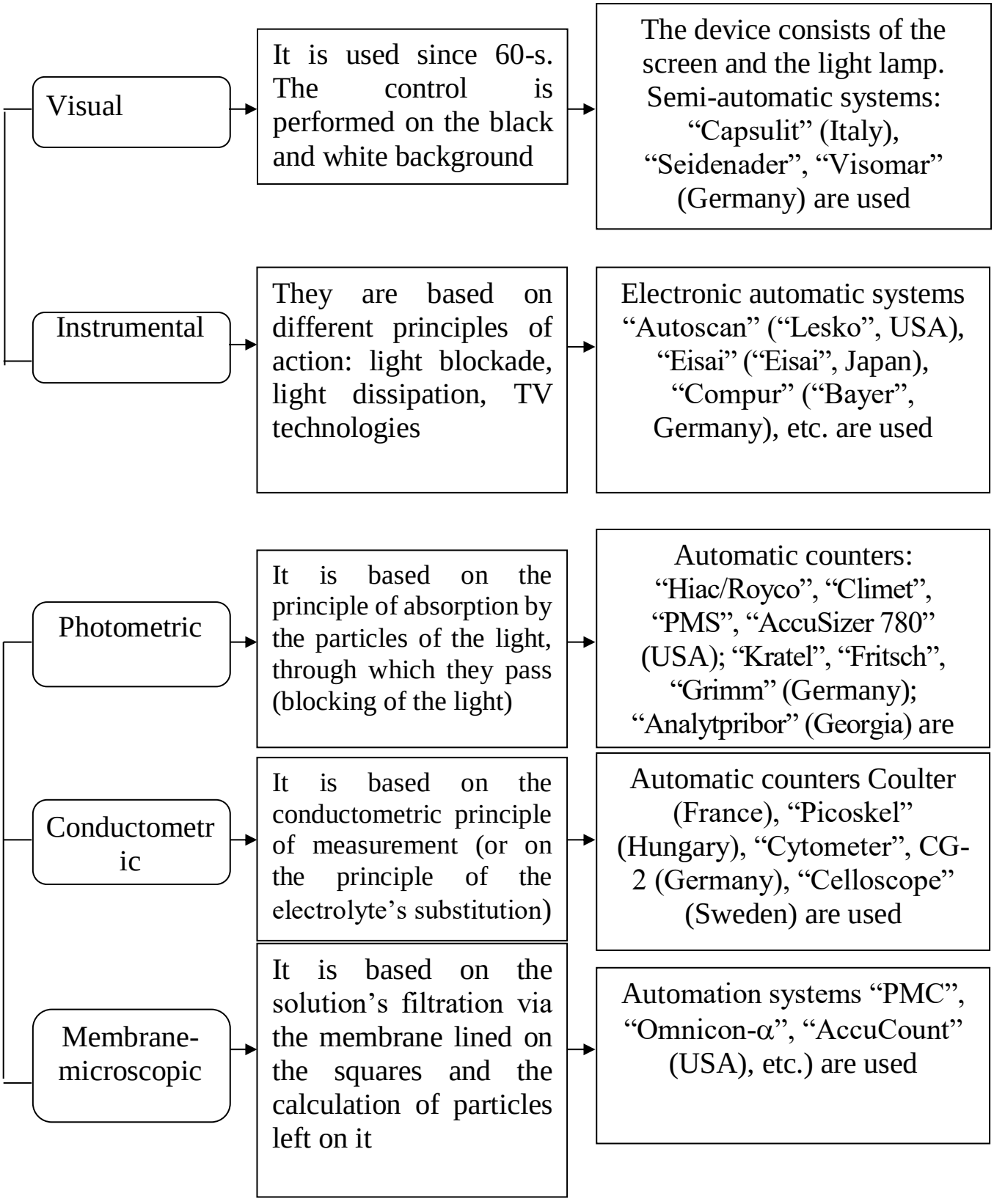
CLASSIFICATION OF METHODS FOR PARTICULATE MATTERS CONTROL IN SOLUTIONS FOR INJECTIONS



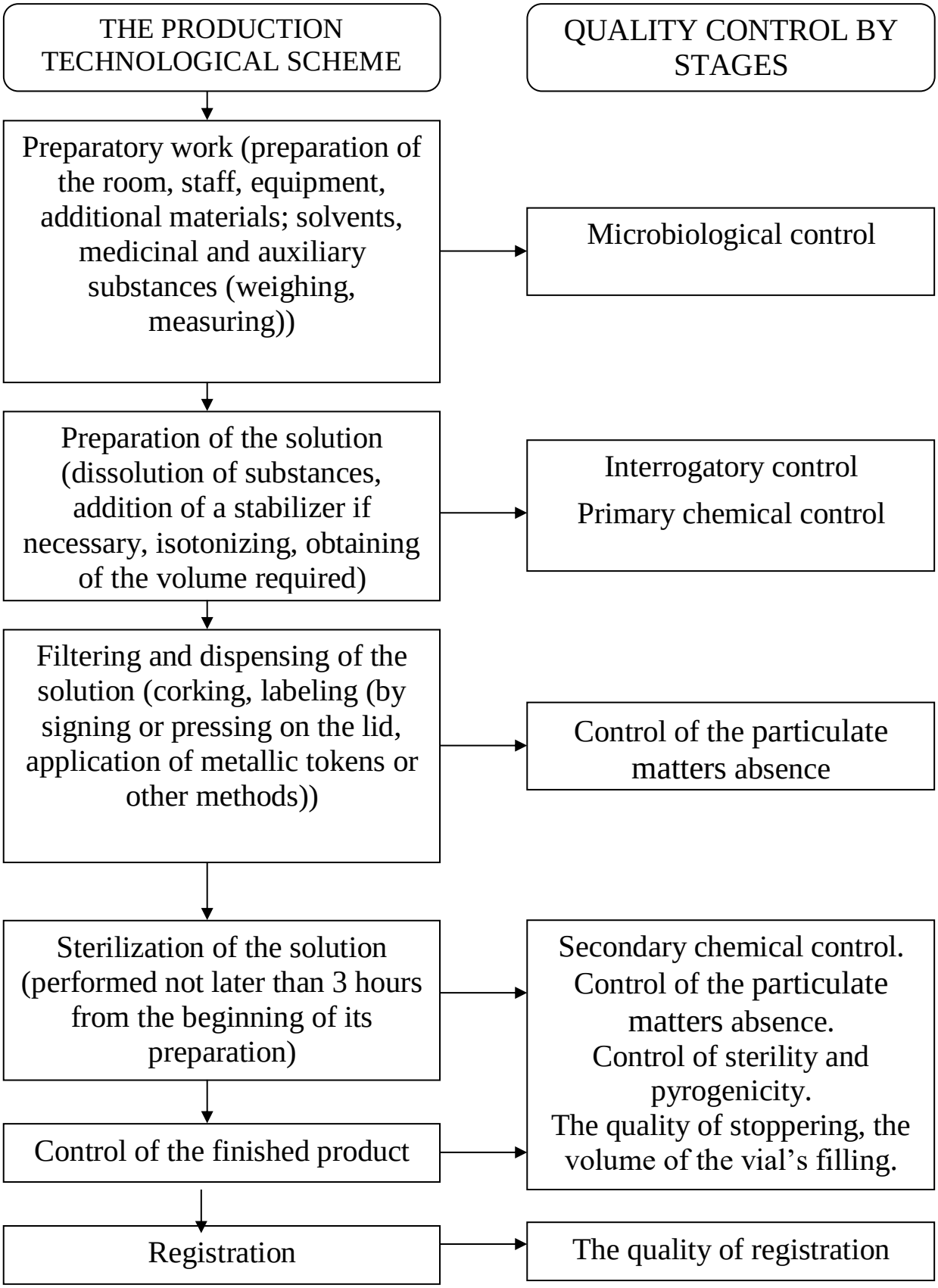
- **The visual method** allows to determine the type and the shape of a particle, identify the bubbles of a gas, and it is impossible when carrying out the instrumental control. **The disadvantage of the method** – it depends on a number of factors: particle's size; the degree of the particles contrast to the background; the quality of light; duration of observation; the type of light; magnification; the personal features of the inspector (visual acuity, the experience of work).
- **The membrane-microscopic method** allows to determine the maximum size of visible and invisible particles and find out their origin. The bubbles of a gas do not affect the control. **The disadvantage of the method** is a large container, high requirements to the inspector's qualification, a considerable period of time for analysis.

7. FORMULATION OF PARENTERAL MEDICINE AND THEIR QUALITY CONTROL

METHODS OF CONTROL OF THE PARTICULATE MATTERS PRESENCE IN SOLUTIONS FOR INJECTIONS



7. FORMULATION OF PARENTERAL MEDICINE AND THEIR QUALITY CONTROL



- The results of the control are registered in the special journal.

7. FORMULATION OF PARENTERAL MEDICINE AND THEIR QUALITY CONTROL

GENERAL RULES FOR PREPARING PARENTERAL MEDICINES

- They can be prepared only at the chemist's shops that have a special permission for preparing medicines given by the authorized organs.
- Heads of the chemist's shops have a personal responsibility for organizing the work in the aseptic blocks and preparing solutions for injections.
- It is forbidden to prepare solutions for injections when the methods of their complete chemical analysis, sterilization mode, data of the chemical compatibility of the ingredients and formulation are absent.
- The simultaneous preparation of several solutions for injections, which include different ingredients, or the same ingredients, but in different concentrations is not permitted.
- Preparation of solutions for injections is performed by the weight and volume method, where a medicinal substance is taken by weight, and a solvent is taken until the definite volume of the solution is obtained.
- Dissolution of medicinal substances is carried out in sterile volumetric flasks. When the glassware for measuring is absent, the amount of the solvent required for preparing a solution is determined by calculation using the density value of the solution with the given concentration or the coefficient of the volume increase.
- In large inter-hospital and hospital chemist's shops dissolution of medicinal substances is carried out in glass 20 liter reactors equipped by electric heating. The process of the liquid's mixing is mechanized with the help of mixers of different type.

7. FORMULATION OF PARENTERAL MEDICINE AND THEIR QUALITY CONTROL

FILTERING AND DISPENSING OF PARENTERAL MEDICINES

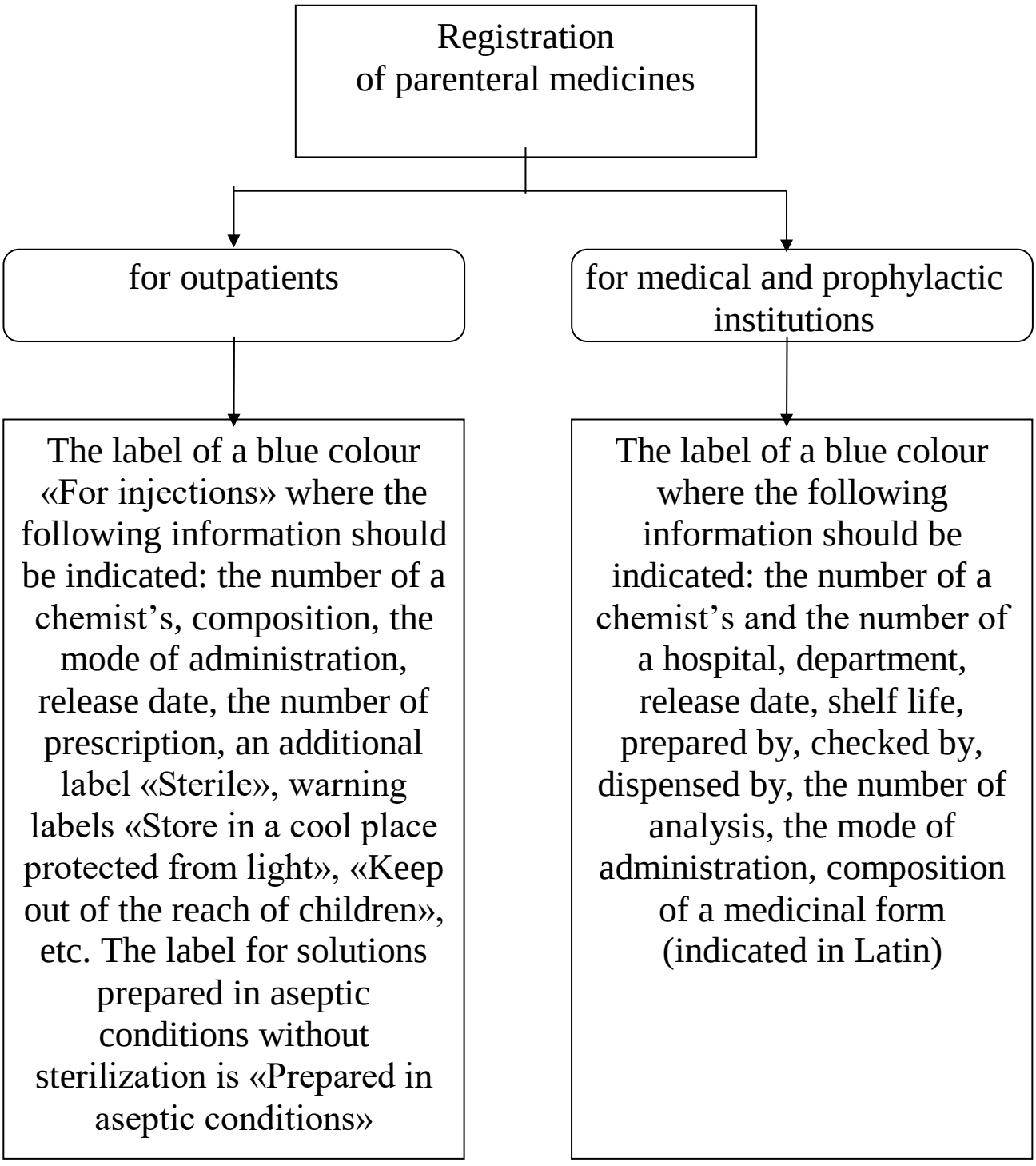
- The main way of filtration of solutions is **vacuum** – its principle is creating rarefaction in the receiver. Under the influence of difference in pressures a liquid passing through the filters fills the receiver.
- The choice of the optimal filtrate is a responsible moment in the formulation of solutions for injections.
- Ashless filters made of filter paper of FO type (M type – filtrating slowly), which retain finely dispersed precipitates are used for filtering.
- Glass filters No.3 and No.4 are widely used.
- A modern way of purification of solutions for injections is membrane microfiltration, which allows obtaining solutions that are free from particulate matters (the particle size is 0.02 μm), visible and invisible, including microorganisms, in visual inspection.
- Filtration of solutions is combined with their simultaneous pouring out into the sterile vials prepared.

PACKING

- Ampoules and vials of glass, polyethylene or other material, which does not change the properties of medicinal substances.
- Dispensing of sterile solutions in wide-necked standard vials (they can be graduated) of different volume with a rubber stopper fixed by the wringed aluminium cap is made from the chemist's shops.
- To cork vials the corks of special sorts of rubber are used: IR-21 (silicon), 25P (natural rubber), 52-369, 52-369/I 52-369/ II (butyl rubber) IR-119, IR-119A (butyl rubber).
- There are reports about the application of polyvinylchloride corks in foreign literature.
- To roll aluminium caps up, as well as to take them off different appliances are offered.

7. FORMULATION OF PARENTERAL MEDICINE AND THEIR QUALITY CONTROL

REGISTRATION
OF PARENTERAL MEDICINES



QUESTIONS FOR SELF-CONTROL

1. Indicate medicinal forms that are required to be prepared in the aseptic conditions.
2. How are aseptic medicinal forms prepared at the chemist's?
3. Give a definition of medicinal forms for parenteral application.
4. Enumerate the requirements to medicines according to the State Pharmacopoeia of Ukraine and the normative documentation.
5. Name the ways of introducing medicinal forms for injections.
6. Name solvents for injection solutions and requirements to them.
7. Enumerate the conditions required for obtaining apyrogenic water at the chemist's and checking its quality according to the normative documentation.

TESTS

1. What is a shelf-live for sterile solutions for injections prepared and closed by aluminum cup in pharmacy?

A 10 days
B 1 month
C 2 month
D 5 days
E 3 month

2. A pharmacist prepared a solution for injection. What the method of sterilization of tableware used for preparation of aseptical medicines?

A Dry air
B Tindalization
C Текучий пар
D Chemical substances
E UV-rays

3. What the method used for the control of parameters while sterilizing by autoclave?

A Thermo-tests
B Stabilizers
C Buffer solutions
D Isotonic agents
D Antioxidants

4. A pharmacy prepares solution fro injections. When it should be checked on the absence of mechanical inclusions?

A Before and after sterilization
B Before filtration
C Before chemical analysis
D After registration for dispensing
E Before and after packing

5. A pharmacist prepares solution for injections. What the amount of bottle should be checked on the absence of mechanical inclusions?

A 50 % of all bottles
B All bottles (100 %)
C 75 % of all bottles
D 25 % of all bottles
E 10 % of all bottles