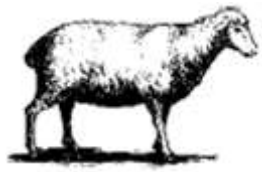
Preparations from animal raw materials. Private technology. Storage conditions and methods of preserving organs and tissues. Technological scheme for obtaining preparations of dried glands and tissues. Dosage forms and standardization. Features of the technology of extraction preparations for internal use. Technological scheme for obtaining drugs for parenteral administration. Highly efficient purification methods: gel filtration, ion exchange, affinity chromatography, etc. Insulin preparations (genetically engineered, pork, beef). Classification of drugs by duration of action (short, medium and long). The ways of prolongation. Highly purified insulin preparations. Insulin "M" and "MS". Insulin standardization. Release form. Automatic insulin dispensers. Private technology.

Lecture for 4th year students of the Institute of Pharmacy of KSMU




Lecture plan

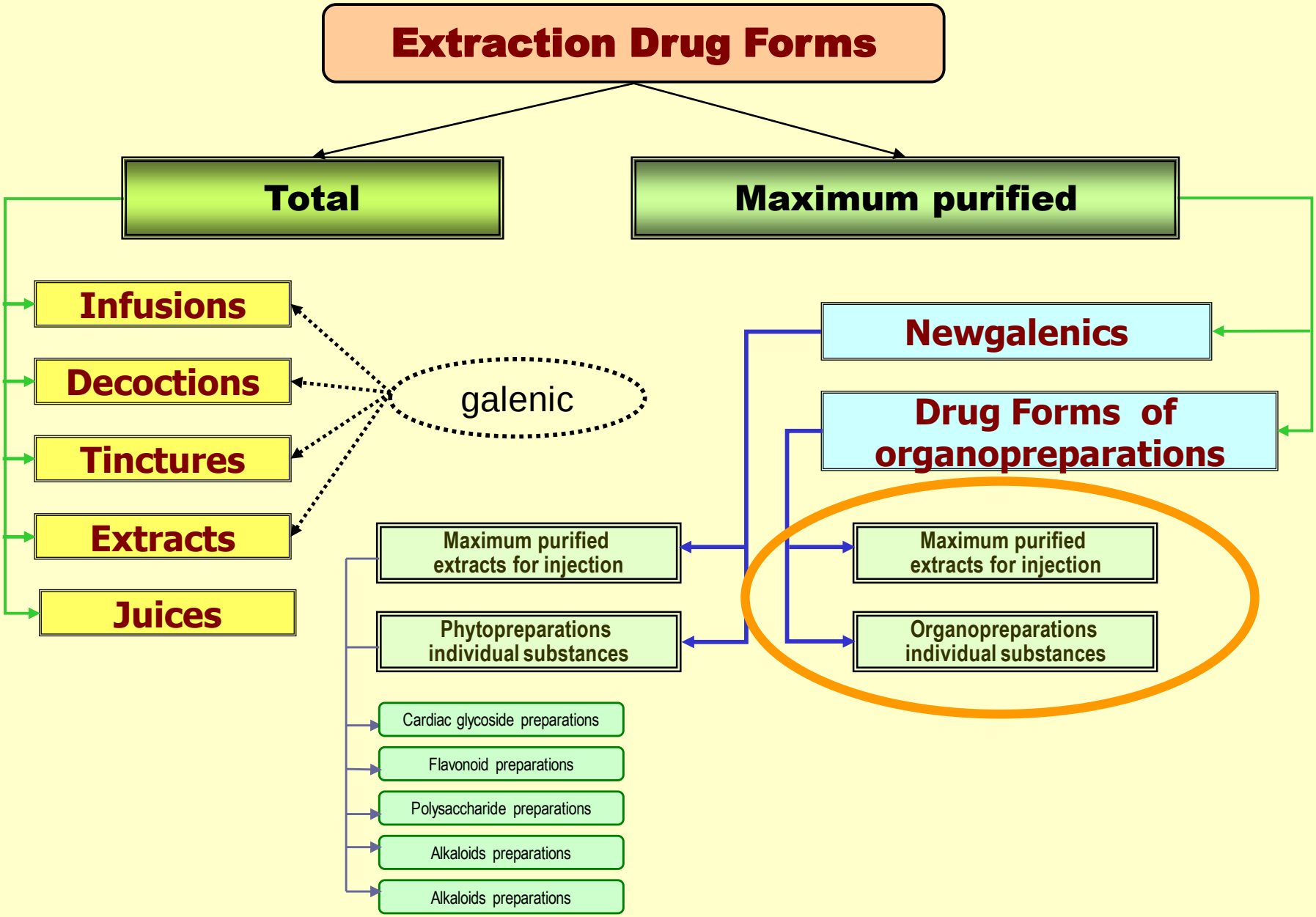
1. Preparations from animal raw materials.
2. Storage conditions and methods of preserving organs and tissues.
3. Technological scheme for obtaining preparations of dried glands and tissues.
4. Private technology. Dosage forms and standardization.

- Features of the technology of extraction preparations for internal use.
- Technological scheme for obtaining drugs for parenteral administration.

5.Highly efficient methods of purification:

- gel filtration,
- ion exchange,
- affinity chromatography, etc.

6.Insulin preparations (genetically engineered, pork, beef). Classification drugs by the duration of action (short, medium and long). The way of sprolongation duration of action of insulin. Highly purified insulin preparations. Insulin "M" and "MS". Insulin standardization. Formulations. Automatic insulin dispensers. Private technology.


Extraction Drug Forms
Total
Maximum purified
Infusions
Decoctions
Tinctures
Extracts
Juices
galenic
Newgalenics
Drug Forms of organopreparations
Maximum purified extracts for injection
Phytopreparations individual substances
Cardiac glycoside preparations
Flavonoid preparations
Polysaccharide preparations
Alkaloids preparations
Alkaloids preparations
Maximum purified extracts for injection
Organopreparations individual substances

Preparations obtained from animal raw materials (organs, tissues, blood, urine, etc.) are called organotherapeutic or organopreparations (Medicamenta organotherapeutica).

The active substances of organopreparations are products of physiological metabolism, contained or accumulated in tissues, organs, biological fluids (enzymes, hormones, vitamins and other substances).

- In raw (unprocessed) form, animal organs are now almost never used for medicinal purposes, since many of them (especially the endocrine glands) deteriorate extremely easily, have an unpleasant taste, have unequal activity, as a result of which their correct dosage is impossible; in addition, it is difficult to supply patients with them on a regular basis.
- Organopreparations are medicines containing some or all of the tissue components, along with differentiated cellular components (for example: cells of various parts of the brain and spinal cord, thymus cells, liver cells, etc.).
- Depending on the level of your integration organopreparations have a substitutional, functional and regenerating effect on tissues - these effects can vary, being combined in different proportions. Actorganopreparations determines their indications for use: they are used primarily in degenerative and chronic diseases, in case of organ failure and in geriatric practice.

CLASSIFICATION OF ANIMAL PREPARATIONS

1. By the method of production and degree of purification - Technological classification

- Dried tissue (gland) preparations
- Extracts for internal use
- Highly purified injection preparations

2. Depending on the nature of pharmacologically active substances, there may be drugs of

- Hormones
- Enzymes
- Vitamins
- Non-specific action

3. Depending on the organ from which they are obtained (by raw materials - body, fabrics, biofluids)

- Preparations of the thyroid, parathyroid, pancreas and other glands
- Drugs liver
- Preparations of the mucous membrane of the stomach, pancreas, testes
- Blood preparations

4. By nature BAS

- Protein preparations
- Peptide preparations
- Acid preparations
- Drugs mucopolysaccharides

The production of organic products is carried out at endocrine plants.

Depending on the production technology, all organic preparations are divided into the following groups:

1. **Dried glands and tissues**. They contain almost completely a complex of substances (active, accompanying and ballast) of the original animal raw materials. *They are produced mainly in the form of powders and tablets.*

2. **Extraction preparations**. They are extracts of active substances obtained as a result of processing raw materials with any solvents (extractants). *With this method of obtaining, the extract is freed from most of the accompanying and ballast substances. Extracts are produced both in dry (powders, tablets) and in liquid form (for internal use).*

3. **The most purified organic preparations.** Pure individual medicinal substances from animal raw materials obtained by deep purification methods (extraction followed by separation of the raw material by adsorption methods on ion-exchange resins, extraction "liquid /liquid"And in other ways). *They are produced mainly in the form of injectable drugs.*

Characteristics of raw materials

1. Health status (veterinary examination)
2. Animal species (cattle, sheep, pigs)
3. Age, season, habitat

Technology features

Low stability	Processing as soon as possible after harvesting
Complex of ballast (proteins, lipids)	Multistage, variety isolation and purification methods
Lability of biologically active substances	"Sparing" mode of the technological process

Features of production and raw materials

In connection with the above, the production of organopreparations are concentrated in meat processing plants, directly at the source of raw materials.

This is explained by the fact that the endocrine glands as raw materials are extremely unstable and quickly lose their active ingredients. Therefore, they must be removed immediately after the slaughter of the animal and immediately sent for processing.

Otherwise, the removed glands should be subjected to **canning**.

Canning is carried out in three ways:

1) immersion in alcohol or acetone (while the raw material is simultaneously dehydrated and partially defatted);
2) salting with dry sodium chloride or its concentrated solution;
3) freezing (the optimal and most common way to preserve raw materials and the medicinal substances it contains).

Dried, fat-free preparations and crushed glands

The process of obtaining drugs in this group consists of the following main technological stages.

BP - 1. Sanitary preparation of production

BP - 1.1. Preparation of industrial premises

BP - 1.2. Processing equipment

BP - 1.3. Sanitary preparation of technological clothing

BP - 1.4. Sanitary training of personnel

BP - 2. Preparation of raw materials

BP - 2.1. Cleaning of raw materials

BP - 2.2. Grinding raw materials

TP - 3. Drying

TP - 4. Degreasing

TP - 5. Standardization

UMO - 6. Packing, packaging, marking

PO - 7. Waste recycling (solvent recovery)

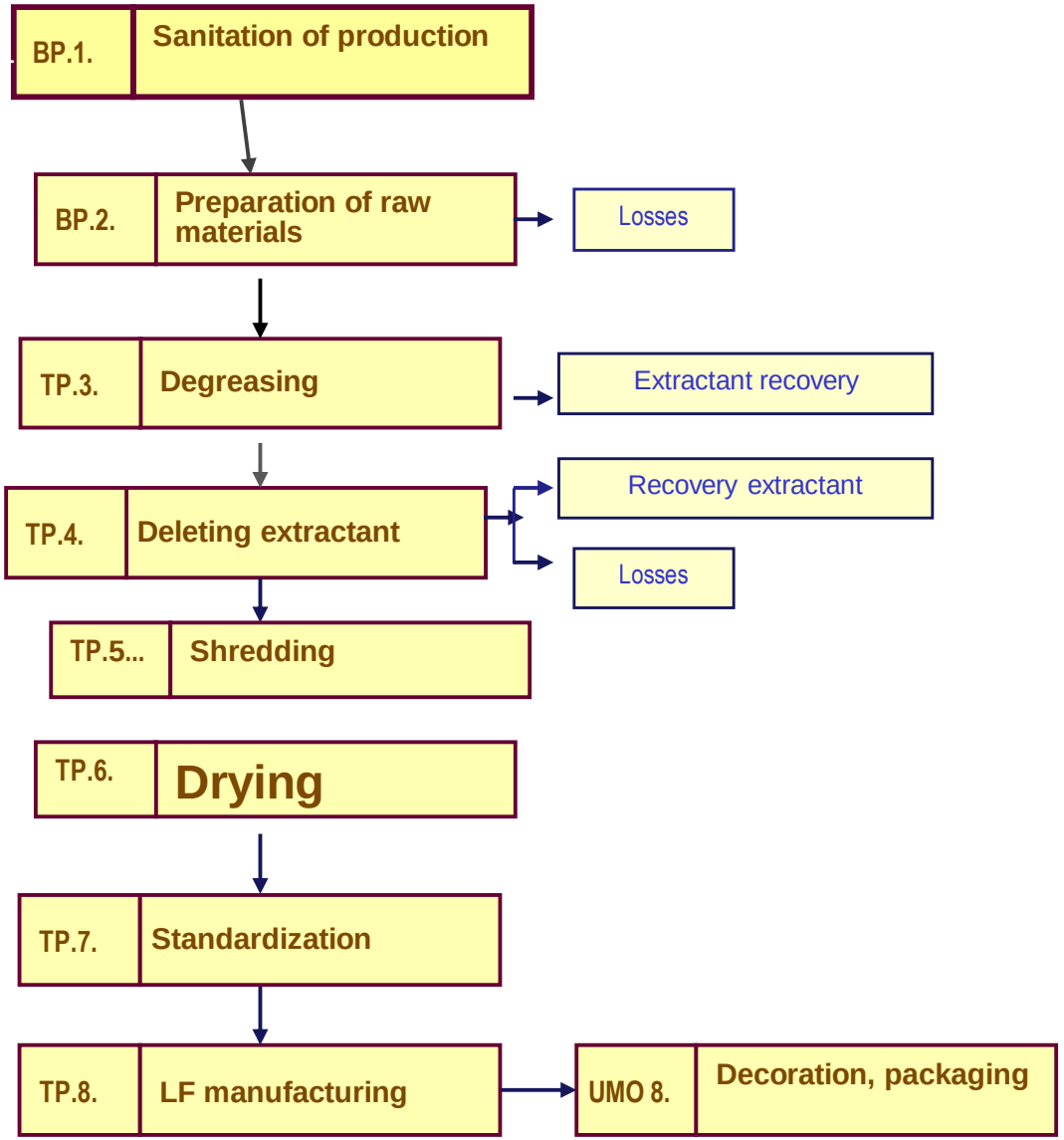
Dried gland preparations include:

Thyroidin (Thyreoidinum) - a preparation of thyroid hormones.

Pituitrin dry (Pituitrinum siccum) - a preparation of hormones of the posterior lobe of the pituitary gland.

Technological scheme for the production of drugs

BP.1.1.	San. room processing
BP.one 2.	San. processing equipment
BP.on e.3.	Staff training
BP. 2.1.	Raw material cleaning
BP.2.2.	Grinding raw materials
BP.2.3.	Drying of raw materials



Standardization. Standardization of preparations of dried fat-free glands is carried out according to the following indicators:

1. Description (appearance, color, smell).
2. Authenticity.
3. Content of biologically active substances (chemical or biological method).
4. Humidity.
5. Microbiological purity.

The drugs in this group were produced in the form of powders and tablets.

So, previously such drugs were produced as adiurecrine and thyroidin. Adiurecrinrepresented the dried, fat-free and powdered posterior lobes of the pituitary gland of cattle and pigs. It was used as an antidiuretic for diabetes insipidus. Currently replaced by a synthetic drugAdiuretin FROMD... Thyroidin - dried, defatted and powdered thyroid gland of cattle and pigs, used internally in case of insufficient thyroid function, is now replaced by a synthetic drugtriiodothyronine...

Extraction organopreparations for internal use

The process of obtaining drugs in this group consists of the following technological stages:

BP - 1. Sanitary preparation of production

BP - 1.1. Preparation of industrial premises

BP - 1.2. Processing equipment

BP - 1.3. Sanitary preparation of technological clothing

BP - 1.4. Sanitary training of personnel

BP - 2. Preparation of raw materials and extractant

BP - 2.1. Cleaning of raw materials

BP - 2.2. Grinding raw materials

BP - 2.3. Dilution of ethyl alcohol

TP - 3. Extraction

TP - 4. Cleaning Extraction

TP - 5. Drying (or precipitation) *

TP - 6. Standardization

UMO - 7. Packing, packaging, marking

PO - 8. Waste processing (recovery of ethanol and other solvents)

- **Note:** the * sign means that this stage is present only in the technology of dry extraction organopreparations for internal use.

Extraction organic preparations for internal use are divided into liquid and dry by consistency.

EXTRACTION

Extraction is a method of obtaining *extraction preparations* and raw extracts during production *the most purified organopreparations.*

The extraction of raw materials is carried out mainly by maceration in apparatuses equipped with stirrers.

When receiving organopreparations of the type **extracts** the hood is subjected to subsequent filtration and settling.

Upon receipt **maximally purified preparations** raw hood is subject to further complex cleaning and separation.

Extraction organic preparations for internal use

No. P/P	Drug name	Raw materials	A kind of drug form	The form release	pharmachologic effect
one	Pantokrin	Non-ossified maral horns	ZhEP of nonspecific action	Liquid in vials; pills	Toning, adaptogenic means
2	Rantarin	Antlers reindeer	ZhEP of nonspecific action	Pills	Toning, adaptogenic agent
3	Pepsin	Pig stomach	SEP enzyme	Tablets in combination with acidin (betaine g /x)	When hypoanacid gastritis
4	Pancreatin	Pancreas gland pigs or cattle	SEP enzyme	Enteric-coated tablets	In chronic pancreatitis with insufficient... pancreatic function

Note: ZhEP - liquid extraction preparation; SEP is a dry extract preparation.

Standardization of liquid extraction organopreparations of preparations is carried out according to the following indicators:

1. Description.
2. The content of biologically active substances (chemical or biological method)
3. Dry residue
4. Ethanol content
5. PH value (for some)
6. Microbiological purity

The most purified organic preparations

By degree of purification of organic products **are subdivided into two subgroups:**

-deeply cleansed

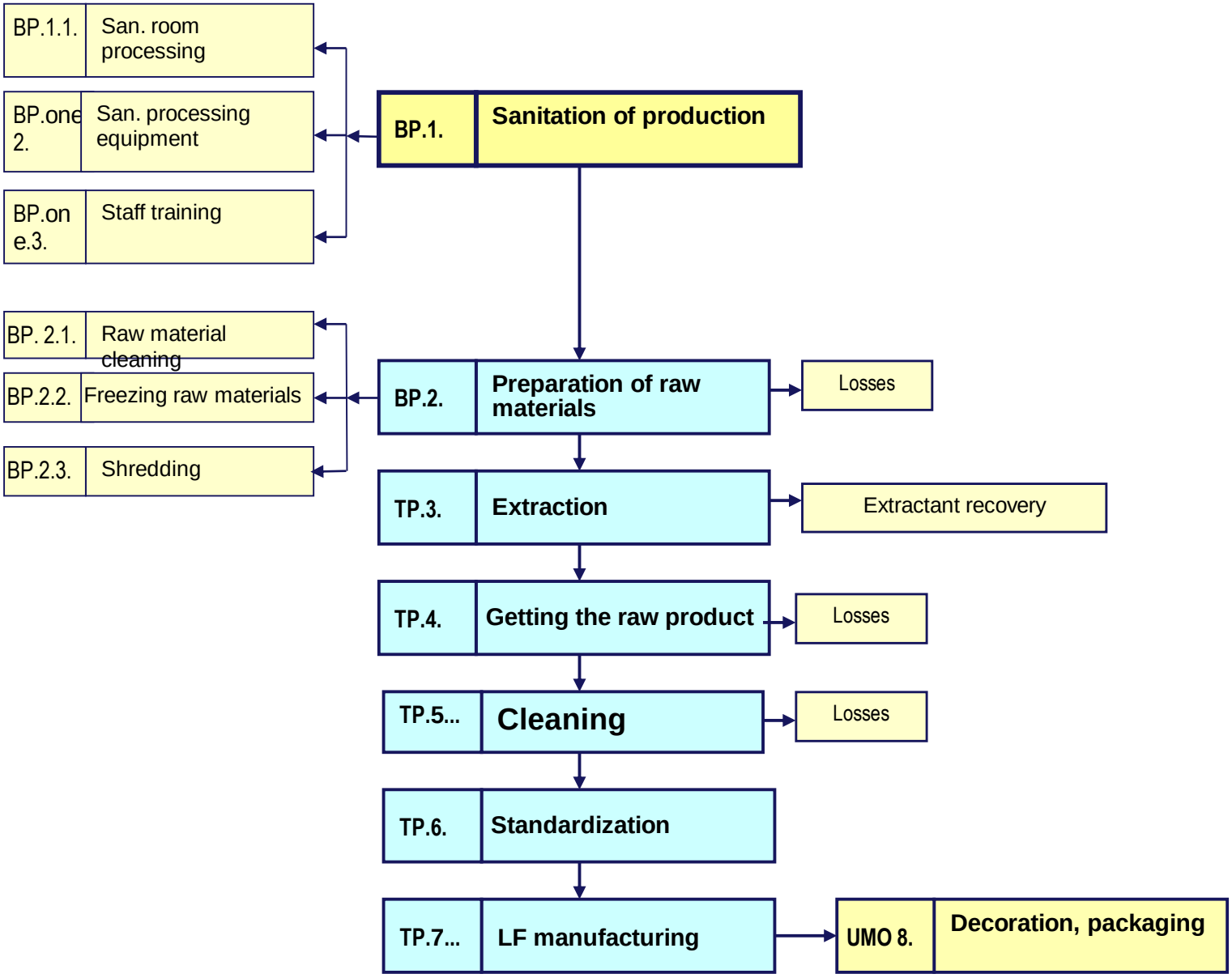
-preparations of individual substances.

Deep purified preparations are organic preparations of the extraction type, in which the primary extract - raw deeply cleared of ballast and related substances and is a combination of active substances. A characteristic difference of these drugs from those listed above is the possibility of their injection...

The specified group of organopreparations is subdivided into:

1. Preparations from animal raw materials containing a complex of biologically active substances, maximally purified from ballast and related substances.
2. Preparations obtained on the basis of individual biologically active substances isolated from raw materials of animal origin.

Production flow chart maximally purified organopreparations



Cleaning methods

A feature of parenteral drugs is deep, maximum cleaning from ballast and related substances. In classical technology, the following types of cleaning are usually provided, the sequence and methods of which can be very diverse:

Rough cleaning

1.Purification from proteins is carried out by the following methods:

- settling extracts in the cold (0-4 ^{0}FROM);
- salting out (i.e., adding heavy metal salts, high concentration ethyl alcohol, tannins);
- bringing to the isoelectric point (by acid-base treatment);
- thermofractionation...

Fat removal is carried out by the following methods:

- settling in the cold (0-4 ^{0}FROM);
-extraction with organic solvents (aviation gasoline, ether).

2.Filtering

Effective (deep)

1. **Fractional sedimentation**

a) change of solvent, $Pb(CH_3COO)_2$

b) alcohol purification, boiling

in) salting out: F^-, $H_2PO_4^-$, $CH3COO^-$, BrO_3^-, Cl^-, ClO_3^- …. CNS^-

Th^{4+}, Al^{3+}, H^+, Ba^{2+}, Sr^{2+}, Ca^{2+},…. K^+, Na^+, Li^+

d) complexation

2. **Liquid extraction**
3. **Separation with membranes**
4. **Sorption chromatographic methods**
5. **Electrophoresis**
6. **Crystallization (recrystallization)**
7. **Sublimation**
8. **Ultrafiltration**

Fractional sedimentation

Fractional precipitation of active or ballast substances can be achieved by changing the solvent. When carrying out extraction with a non-polar or low-polarity (organic) solvent, the extraction is purified from hydrophobic substances (chlorophyll, resins anddr) is achieved by removing (distilling) extractant and adding water to the remainder. At the same time, the solubility of hydrophobic substances decreases, they precipitate and are removed by filtration or centrifugation. Adding toethanol solutions of ether, precipitate and remove saponins (cardenolides remain in solution). Proteins, pectins, mucus and other hydrophilic biopolymers are precipitated by the introduction of ethanol in a concentration of at least 50% to aqueous extracts. Extracts partially purified from biopolymers are obtained by direct use asextractantethanol in a concentration of at least 70%. Ethanol, being hydrophilic, takes away natural IUDs from molecules in solutionhydrated shell, causes their deposition, and at the same time hydrated... For selective "salting out»High molecular weight compounds (proteins, gum, mucus, pectins) use solutions of neutral salts. Mechanismsalting out is that the added anions and cations of the salt solution hydrated, taking away water from biopolymer molecules, promoting their adhesion and sedimentation. Ability tosalting outmost pronounced in salt anions. According to the strength of the salting-out effect, anions and cations are arranged in the following rows of decreasing activity...

$$SO_4^{2-} > C_6H_5O_7^{3-} > CH_3COO^- > Cl^- > NaO_3^- > Br^- > I^- > CNS^-$$

$$Li^+ > Na^+ > K^+ > Pb^+ > Cs^+$$

These rows are called lyotropic... effect.In practice, forsalting out more often sodium sulfate or sodium is used or ammonium chlorides.

Preparations of individual substances

If deeply purified preparations contain the amount of active substances, then this group of organic preparations includes **absolutely clean** (without impurities, in most cases **crystalline**) individual substances.
The name "organopreparation" indicates only the source of the substance. Currently, many drugs of this type (insulin, oxytocin, adrenaline, prostaglandins) are obtained synthetically.

INSULINS

- **Pork**
- **Cattle** (beef)
- **Human** (semi-synthetic or biosynthetic)

Conventional – more than 10,000 molecules of proinsulin per 1 million insulin

Monopoke - less than 3000 molecules of proinsulin per 1 million insulin

Improved Monopoke - less than 50 molecules of proinsulin per million insulin

Monocomponent - less than 10 molecules of proinsulin per 1 million insulin

- **Fast and short acting**
- **Average duration of action**
- **Long-acting**

Release of insulin from pancreatic acid

1. Grinding the glands

↓

2. Extraction (ethanol, acidified ethanol solution)

↓

3. Defending (precipitation of proteins in the cold)

↓

4. Centrifugation

↓

5. Ion exchange chromatography (sulfonic cation exchanger, pH 3-3.3)

↓

6. Washing (fat ethanol, protein acetate buffer pH 5.3)

↓

7. Desorption of insulin ammonium buffer pH 10

↓

8. Sedimentation of ballast from solution (pH 4.5 + acetone)

↓

10. Insulin deposition (zinc acetate pH 6.2)

↓

12. Dissolving insulin in water (pH 2.8)

↓

13. Deposition and filtration (via gizelguhr)

↓

14. Crystallization of insulin (+ $ZnCl_2$ 0^0C pH 8.5 → 5.8)

↓

14. Washing insulin crystals (water, acetone, ether)

Protamin-zinc-insulin for injection (Protamin-Zinc-insulinum pro injectionibus)

The drug obtained by adding crystalline insulin to a solution solution of protamine, zinc chloride and sodium phosphate. Also contains glycerin and phenol. It is active up to 20 hours after administration.

Suspension of insulin-protamin for injection (Suspensio Insulin-protamin pro injectionibus)

Sterile suspension of insulin crystals in complex with protamine in phosphate buffer. Also contains antimicrobial agents. Active for 18-30 hours after administration.

Suspension of protamine-zinc-insulin for injection (Suspensio Protamin-zinc-insulini pro injectionibus)

It is obtained by adding protamine sulfate, zinc chloride and sodium phosphate solution to the crystalline insulin solution. The suspension contains antimicrobial agents and acts within 24-36 hours after administration.

EXAMPLES OF ORGANOPREPARATIONS OF DIFFERENT GROUPS

Adiurecrin... Dry pituitrin (Adiurecrinum... Pituitrinum siccum)

A preparation of the posterior lobe of the pituitary gland, obtained from that of cattle and pigs. Fine grayish powder. Practically insoluble in water and common solvents. Contains hormones of the posterior pituitary gland, in particular antidiuretic hormone. The activity of the drug is determined by the biological method: 1 mgadiurecrina contains 1 UNIT.

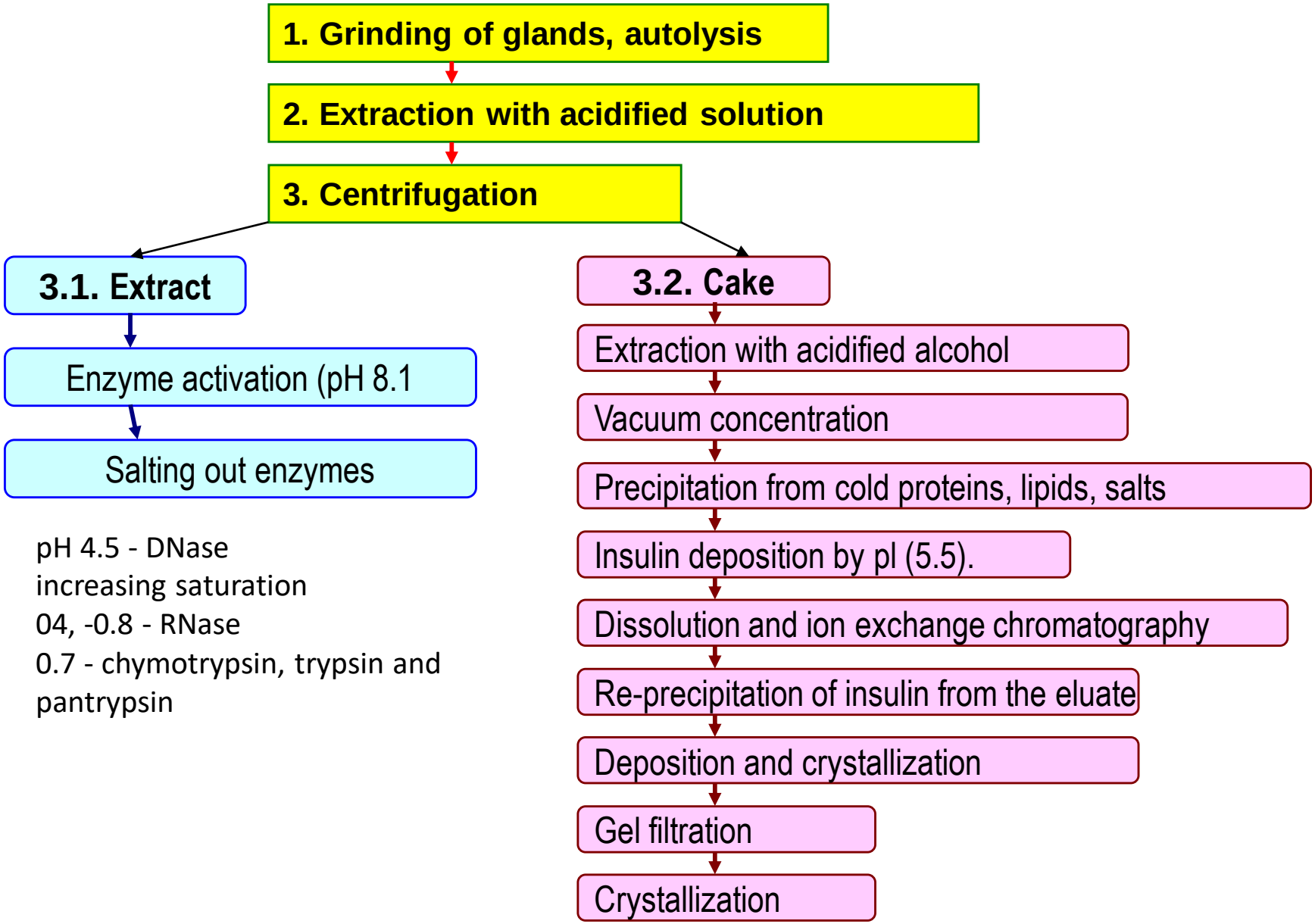
Thyroidin dry powder (Thyreoidinum siccum)

Thyroid hormone preparation. It is a yellow-gray powder with a faint odor characteristic of dried animal tissues. Insoluble in water, alcohol and other solvents. Possesses the biological activity of the thyroid hormone. It is standardized by the content of organically bound iodine, the content of which in the preparation should be from 0.17 to 0.23%.

Pantokrin (Pantocrinum)

Liquid alcoholic extract from non-ossifiedantlers (antlers) of maral, red deer and sika deer. Transparent, colorless or slightly darkish liquid with a phenol odor. Also available in the form of tablets prepared from the mass formed by evaporation of the liquid extract...

Complex processing of the pancreas



Pancreatinum

Enzyme preparation from the pancreas of slaughter cattle. Amorphous fine yellowish powder obtained by extracting the pancreas with water, acidified with hydrochloric or acetic acid, followed by drying the liquid extract under vacuum. The powder is slightly soluble in water, insoluble in alcohol and other solvents. Contains mainly trypsin and amylase. It is standardized by the biological method: in 1 g 25 U.

Pepsin (Pepsinum)

A preparation containing a proteolytic enzyme. Received from the mucous membrane of the stomach of pigs by extraction of water acidified with hydrochloric acid, followed by drying under vacuum. During standardization, the powder is mixed with milk or beet (less commonly) sugar, after which it acquires a white or slightly darkish color and a sweetish taste. Has a peculiar smell. Let's dissolve in water and 20% alcohol.

Acidin-pepsin (Acidin-pepsinum)

Tablets containing 1 part pepsin and 4 parts betaine hydrochloride.

Synthetic drugs

Currently, a number of drugs, previously produced by extraction of the corresponding organs and tissues, are obtained synthetically. These include synthetic analogs
-***adrenal cortex hormones***,
- ***female and male sex hormones, corpus luteum hormones (gestagens and progestins)*** and etc.

Methyltestosterone (Methyltestosteronum)

A synthetic analogue of testosterone. It is a white crystalline powder, odorless and tasteless. Available in the form of tablets of 0.005 and 0.01 g.

Progesterone (Progesteronum)

Synthetic hormone of the corpus luteum. It is produced in the form of an injection oil solution of 1% and 2.5% in 1 ml ampoules.

Estradiol benzoate (Oestradioli benzoas)

0.1% oil solution in ampoules of 1 ml, intended for intramuscular administration.

Sinestrol (Synoestrolum)

Synthetic estrogenic drug of non-steroidal structure, which is a derivative of stilbene. Flavourless white or slightly yellowish powder. Available in 0.01 g tablets, 1 ml ampoules with an oil solution containing 0.1% (1 mg in 1 ml) and 2% (20 mg in 1 ml) of the drug.