ВОЛГОГРАДСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

Drugs obtained from human and animal blood and plasma. The history of development and application. Virus security.

Biological drugs

- *medicinal products, the active substance of which is produced or isolated from a biological source and a combination of biological and physico-chemical methods is necessary to determine the properties and quality of which.*
- *biological medicines include immunobiological medicines, medicines derived from blood, human and animal blood plasma (with the exception of whole blood), biotechnological medicines, gene therapy medicines*

Term of biological medicines

The European Union	The Russian Federation (FZ-61 dated 12/22/14)
biosimilar drug (biosimilar) a biological medicinal product that contains a version of the active substance of a registered biological original (reference) drug and for which similarity (similarity) has been demonstrated based on comparative studies with the original medicinal product in terms of quality, biological activity, efficacy and safety	biosimilar medicinal product (biosimilar) a biological medicinal product similar in terms of quality, efficacy and safety to a reference biological medicinal product in the same dosage form and having an identical method of administration

Differences between drugs of chemical and biological nature

Indicator	Chemical drugs	Biological drugs
Molecular weight	Low – less than 1 kDa	High – more than 1 kDa
Origin	Chemical synthesis substances (xenobiotics)	Similar to the proteins of the human body
Stability	Stable	Thermosensitive
Chemical structure	Well characterized, homogeneous	Heterogeneous composition
Metabolism	Metabolism with the formation of active and inactive products	Catabolism as endogenous proteins
The role of cytochrome P450 in metabolism	Participates	does not participate
The route of administration	The oral method of administration prevails	Parenteral

Biological/biotechnological preparations have an advantage in comparison with chemical preparations

- treatment of many diseases is possible only with biological / biotechnological drugs (hemophilia, pituitary nanism, diabetes mellitus, anemia, allergies, etc.);
- biological / biotechnological drugs have a targeted (directed) effect; biological/biotechnological preparations are almost nontoxic (metabolism as in endogenous proteins);etc.

Features of the production of biological products

1 Unique cell line from different living systems from E.coli and yeast to transgenic animals and plants.

2 Post-translational modifications.

3 The protein is easily susceptible to foreign contamination.

4 Minimal deviations in the production process cause large changes in the characteristics of the drug.

5 The risk of developing immunogenicity is associated with the characteristics of the drug (protein structure, n/a modifications, aggregates, impurities).

6 The need for comparability studies after changes in the production process.

7 Significant individual variability of effects.

8 Different safety indicators when used for different indications.

The history of creation and development

1840 For the first time, blood transfusion was performed to a boy with hemophilia A and uncontrolled bleeding

1923 Eli Lilly established the production and release of insulin of animal origin

1939 Transfuso Vac container (storage of blood for up to 21 days)

1942 Cutter introduced plasma fractionation and developed a method for producing albumin Albumin is the first blood drug

1959 Pool and Robinson found that when frozen plasma is thawed, the resulting sediment contains most of the plasma's antihemophilic activity

Cryoprecipitate is the second blood preparation

1968 The first factor VIII drug

1979 Automated Shaped Element Separator

The history of creation and development

1981 The first drug of intravenous immunoglobulin (Miles Inc., Gamimun)

1982 Eli Lilly established the production and release of insulin of human origin (genetically engineered)

1982 Factor VIII drug treated with dry heat

1983 Heat treatment as a method of inactivation of viruses

1983 Oktafarma Company received a patent for a solvent-detergent treatment technology

1985 The preparation of factor VIII Octa B, which has been treated with a solvent detergent

1986 The first drug (mouse antibody) created using hybridomic technology — Orthoclone OKT3 (muromonab-CD3) - was intended to reduce immune rejection during organ transplantation.

1987 The FDA approved the enzyme Alteplase for use

The history of creation and development

1988 Factor VIII preparation purified with monoclonal antibodies

1992 Widespread introduction of solvent-detergent treatment as an effective method of inactivation of enveloped viruses

1994 Recombinant glucocerebrosidase (imiglucerase) was introduced for the treatment of Gaucher disease (produced using Chinese hamster ovarian cells)

1994 The first chimeric therapeutic monoclonal antibody that appeared on the market, abcximab, was intended to prevent platelet aggregation during surgical interventions

1998 the first humanized antibody "Herceptin" (trastuzumab) is a drug that targets the supersynthesized HER2 receptor in order to treat an aggressive and deadly form of breast cancer

2002 Adalimumab is the first fully human antibody that binds and inhibits tumor necrosis factor (TNF), a key pro—inflammatory cytokine.

2011 Several monoclonal antibody preparations capable of binding to immune response control points — pembrolizumab, nivolumab and ipilimumab have been approved for use

How are drugs created?

Plasma is the main material for the creation of blood products.

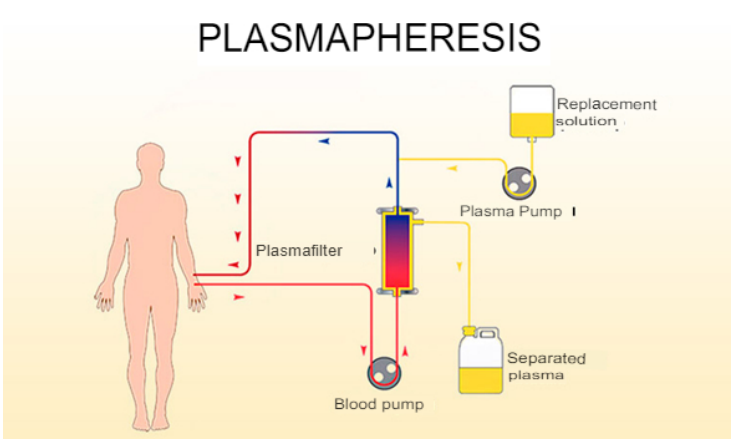
Two ways to obtain freshly frozen plasma:

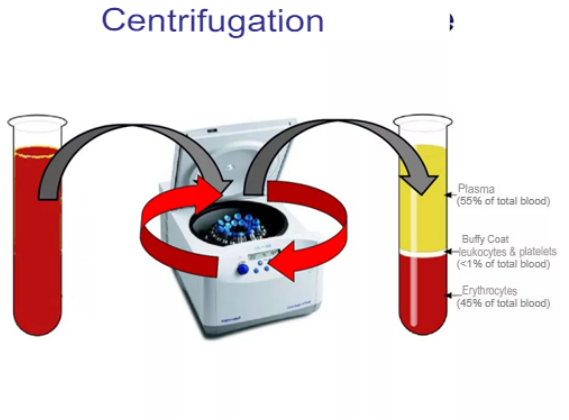
plasmapheresis (a procedure in which part of the collected blood is returned to the donor);

centrifugation of whole blood.

Plasma can be stored for up to three years and thawed at a temperature of 35-37 ° C before use.

Finished drugs are produced by pharmaceutical companies and sometimes by blood centers.

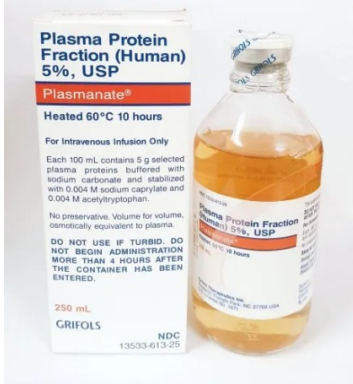




What are blood protein preparations for?

Protein preparations include albumin and protein. They are necessary for traumatic and surgical shocks, burns, cirrhosis of the liver.

Albumin is used for damage to the gastrointestinal tract and many other diseases.



Protein is needed to increase blood pressure and is necessary in the postoperative period to increase the protein content in the body. In case of severe blood loss, this drug is additionally combined with a transfusion of donated blood.

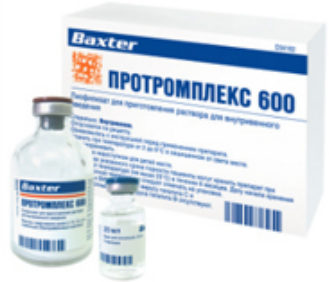
How are blood coagulation correctors used?

Cryoprecipitate, prothrombin complex, thrombin — this is not the whole list of drugs that correct blood clotting.

Patients with hemophilia A need cryoprecipitate (this is a hereditary disease that manifests itself as non-coagulability of blood)

In the prothrombin complex — patients with hemophilia B

Thrombin is needed to stop capillary bleeding.



How will immunological blood products help?

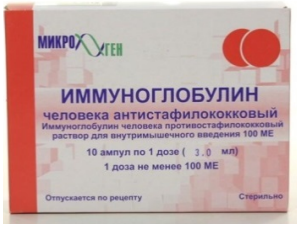
Gamma globulin and polyglobulin are drugs necessary for the prevention of measles, infectious hepatitis, whooping cough, polio, tetanus and tick-borne encephalitis.

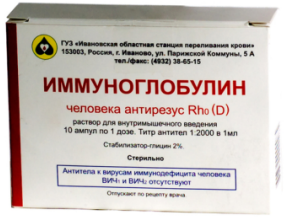
Antistaphylococcal gamma globulin is needed for adults and children with staphylococcal sepsis, osteomyelitis and peritonitis.

Antiresus gamma globulin is used in Rhesus conflict between mother and fetus.

Gamma globulin anti-influenza is used to treat influenza, including its toxic forms.

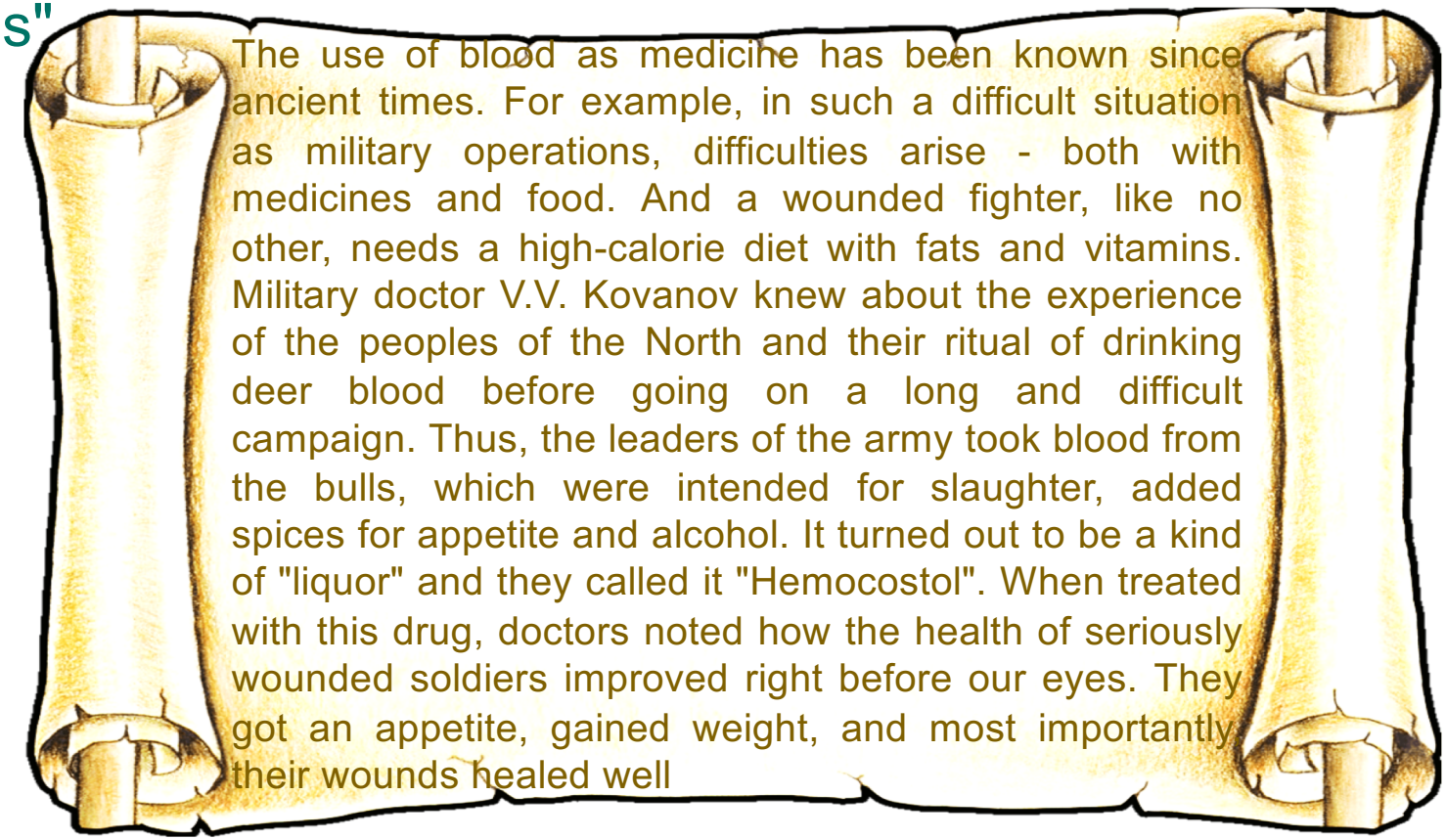
Immunoglobulin against tick-borne encephalitis





Medicines from animal blood

The problem of medicines that are produced from the blood of various animals is of great concern to a large number of doctors, scientists and patients around the world today. The reason for this is the high risk of transmission of infections and so-called "prion diseases"



The use of blood as medicine has been known since ancient times. For example, in such a difficult situation as military operations, difficulties arise - both with medicines and food. And a wounded fighter, like no other, needs a high-calorie diet with fats and vitamins. Military doctor V.V. Kovanov knew about the experience of the peoples of the North and their ritual of drinking deer blood before going on a long and difficult campaign. Thus, the leaders of the army took blood from the bulls, which were intended for slaughter, added spices for appetite and alcohol. It turned out to be a kind of "liquor" and they called it "Hemocostol". When treated with this drug, doctors noted how the health of seriously wounded soldiers improved right before our eyes. They got an appetite, gained weight, and most importantly their wounds healed well

Medicines from animal blood

«Actovegin» is a deproteinized hemoderivate of calves' blood. A drug that activates metabolism in tissues, improves trophism and stimulates the regeneration process. An antihypoxant that has three types of effects: metabolic, neuroprotective and microcirculatoryAs part of complex therapy: cognitive impairment, including post-stroke cognitive impairment and dementia; peripheral circulatory disorders and their consequences; diabetic polyneuropathy.

«Solcoseril»is a deproteinized hemodialysate containing a wide range of low molecular weight components of the cell mass and blood serum of dairy calves with a molecular weight of 5000 D. A drug that improves trophism and tissue regeneration. It is used for minor injuries (abrasions, scratches, cuts); 1st and 2nd degree burns (sunburn, thermal burns); frostbite; difficult-to-heal wounds (including trophic ulcers and bedsores).

Medicines from animal blood

"Hematogen" is produced from defibrinated dry blood of cattle. A source of complete protein, fats, and carbohydrates. Minerals and all amino acids are contained in an optimal ratio for the body. The drug increases the hemoglobin content in the blood, improves the morphological characteristics of red blood cells. It stimulates hematopoiesis, promotes iron absorption in the intestine, increases the hemoglobin content in the blood, increases the ferritin content in plasma.

It is used for malnutrition; iron deficiency anemia; during the period of convalescence of diseases.

Fibrin films (or hemostatic sponges) are obtained from stabilized blood of cattle or pigs. When applied to the wound surface, they create favorable conditions for tissue regeneration, contributing to rapid wound healing. They have an analgesic effect, isolate skin receptors from various irritants and protect the wound from mechanical damage and infection.

Indications: capillary and parenchymal bleeding (from various organs and tissues), bleeding from the sinuses of the dura mater, alveolar bleeding; bleeding against the background of dental interventions; trophic ulcer, bedsores, wounds, TBI; filling defects of parenchymal organs; prevention of adhesions during abdominal operations; covering extensive scalped wounds of the skin of traumatic origin, especially with a tendency to increased bleeding.

Unwanted effects of blood-derived drugs

Accelerated elimination of the drug

Decreased effectiveness (neutralizing antibodies)

Development of allergic reactions

The problem of the safety of blood drugs

Speaking about the safety of blood products, it should be borne in mind that this problem must be considered from two positions:

- guaranteed absence of pathogens of hemotransmissive infections in the preparations (HIV 1, 2, hepatitis B virus, hepatitis C and other microorganisms)
- ensuring a minimum manifestation of the side effect caused by the effect of the drug as such

Virus security

During production, medicines may be exposed to viral contamination.

The risk of viral contamination is possible for all medicines in the production of which raw materials and materials of animal or human origin are used.

The main causes of its occurrence are the use of infected materials (raw materials, cell cultures) and accidental introduction of the virus during the production process.

The risk of viral contamination is possible for drugs produced from:

- blood, urine and other biological fluids of humans or animals;
- from human or animal organs and tissues;
- using the in vivo cultivation method;
- in vitro cultivation of human or animal cell lines.

The general pharmacopoeia article does not apply to non-traditional vector-borne agents, such as pathogens of transmissible spongiform encephalopathy of cattle and scrapes (scratching) of sheep and goats.

The requirements for ensuring viral safety for drugs obtained using materials of human or animal origin are established by the authorized body in accordance with the requirements of the current regulatory legal acts of the Russian Federation

Risks of viral contamination

The main causes of virus contamination of medicines:

- the use of raw material obtained from an infected person or animal;
- extraneous viruses introduced in the process of drug production;
- the use of contaminated reagents and animal products in the production of medicines;
- infected donor cells and cell lines contaminated with viruses prior to their use as GBCs and RBCs;
- a contaminating virus introduced during the creation of a production cell line under improper conditions.

To ensure the viral safety of drugs during production, the following measures should be carried out:

1. selection and testing of raw materials and the source of materials for the absence of viruses pathogenic to humans;
2. assessment of the possibilities of inactivation and/or elimination of the viral agent during the production process;
3. conducting tests for the absence of viral contamination at critical stages of production.

At the same time, it should be borne in mind that none of these measures provides a complete guarantee of the absence of viruses, therefore it is necessary to use an integrated approach. Measures taken to manage the risk of viral contamination of drugs, in the production of which raw materials and materials of animal or human origin are used, are reduced to minimizing the risk, rather than eliminating it. Any residual risk should be assessed in connection with the possible benefits of using a particular material or raw material in the production of drugs.

Requirements for raw materials

To minimize the risk of viral contamination, the following conditions must be observed when selecting raw materials and supplies:

1. Raw materials of human origin (blood, urine, or other human biological fluids) are harvested from healthy donors. Donors of blood and blood plasma, urine, or other biological fluids must be examined in accordance with regulatory legal documents in force in the territory of the Russian Federation.
2. Raw materials of animal origin should be selected only from animals from farms that are safe for infectious diseases. Raw materials must be subject to mandatory veterinary and sanitary examination in accordance with the requirements of regulatory legal acts in force on the territory of the Russian Federation and accompanied by appropriate supporting documents.
3. It is necessary to determine the genus and source of origin of animals intended for the production of biotechnological medicines, including genotype and age. Animals must be taken from closed-type farms that are safe for infectious diseases. The status of the farm must be confirmed by appropriate documents.
4. Materials and reagents of biological origin (such as sheep erythrocytes, calf embryo serum, bovine serum albumin, human transferrin, insulin, trypsin, etc.), nutrient media used in the production of medicines must be free from viral contamination and have the necessary quality.

The processes of viral inactivation or elimination

If necessary, viral elimination and / or inactivation of viruses in the composition of drugs, the raw materials and materials are processed by the following methods:

physical sterilization, steam treatment, dry heating, radiation, filtration; (sterilization with saturated steam under pressure, hot air, filtration, ionizing radiation);

chemical (destruction of the supercapsid of enveloped viruses containing lipids using detergents);

combined (neutralization with specific antibodies, removal of viruses by chromatographic methods, heating in the form of a suspension with chemical agents and others).

Any of the treatment methods used must be validated and must provide a significant reduction in the risk of viral contamination of medicines during their production.

Methods used to inactivate or eliminate viruses

Way	The essence of the method	Limitations of the method
Pasteurization of the liquid product	Heating of the product at a temperature of 60 ° C in a liquid state for 10-12 hours	The risk of infection with hepatitis B and C viruses exists when using pasteurized concentrates; the need to use high concentrations of protectors, mainly carbohydrates with various additives, to protect labile plasma proteins from denaturation. At the same time, they stabilize viruses
Chemical inactivation of the virus in a liquid product	It is based on the ability of chemical substances to destroy the lipid membrane of viruses. The use of solvents (solvent-detergent method; SD-method) to remove the lipid envelope	The use is limited due to the lability of plasma proteins. The method is used for inactivation of viruses having a lipid envelope. It is ineffective for inactivating viruses that cause hepatitis A or parvovirus infection. The SD method is banned in the USA due to its association with the development of thrombosis in individual patients. It can lead to a decrease in the biological activity of the drug and to the formation of autoantibodies. For example, a method using methylene blue reduced the activity of fibrinogen by 65%; blood coagulation factor VIII by 67%
Chemical treatment + ultrafiltration of the product	Joining the chemical treatment of the ultrafiltration method	The need to remove the decay products of viruses requires the introduction of additional stages of purification of the blood preparation
Ultraviolet + chemicals	Plasma and its preparations are irradiated with light in the ultraviolet range in the presence of small concentrations of chemical substances - dyes (methylene blue, etc.)	The method is applicable for inactivation of viruses with a lipid envelope. It is ineffective for inactivating viruses that cause hepatitis A or parvovirus infection. The removal of virus decay products requires additional steps. Partial denaturation of therapeutic proteins and the formation of autoantibodies to them is possible
Lyophilization treatment with steam	The lyophilizate is treated with hot steam in a closed system filled with an inert gas under pressure for 1-10 hours	Hepatitis B virus was detected in some drugs
Dry heating of lyophilosate	Inactivation of viruses occurs when lyophilizate is heated at a temperature of 68 ° C for 32-60 hours	Hepatitis B, C and HIV viruses were preserved in concentrated monogeneous preparations
Rigid heat treatment of lyophilizate	Warming up to a temperature of 80 ° C for 72 hours	Protectors are required, partial denaturation of proteins is possible. It is possible that viruses causing hepatitis A or parvovirus infection may remain in the preparation
Chromatography (gel filtration, affinity and ion exchange chromatography)	The separation occurs as a result of the inter-molecular interaction of the virus envelope proteins with the sorbent	Chromatographic methods are ineffective in removing shell- free viruses. They are usually used to obtain minor proteins from blood plasma
Ultrafiltration	Mechanical separation of viruses due to their larger sizes than plasma proteins . The method is effective for removing both enveloped and non-enveloped viruses. Filters with a pore size of 15-20 nm make it possible to separate hepatitis A virus and B19 virus from factor IX	It is used as a stage of multi-stage methods of blood purification from viruses. The particle sizes of the virus causing hepatitis A are in the range of 25-30 nm; the B19 virus is in the range of 18-26 nm; the virus causing hepatitis C is 28-30 nm; the sizes of viruses of the herpetic family are in the range of 120-300 nm; the HIV capsid is 100-120 nm
Ultrashort laser pulses (wavelength 425 nm)	Destruction of viruses in a liquid medium. It is also effective for removing enveloped and non-enveloped viruses	No data available

The processes of viral inactivation or elimination

Currently, all the problems that arise when obtaining medical preparations from human blood plasma and animal blood serums cannot be considered overcome.

The analysis of technologies for obtaining such drugs by "advanced facilities" shows that the industry is constantly searching for new ways to purify plasma proteins that would be more gentle and guarantee the viral safety of drugs.

At the same time, it is impossible not to notice the exhaustion of opportunities for further development of basic technologies for the purification of blood products beyond private improvements.

At the same time, technologies are being developed that eliminate the need to work with donated blood and hyperimmune sera of animals, allowing to obtain blood preparations using genetic engineering technologies.

The drugs themselves are fundamentally changing. Recombinant blood clotting factors with altered properties are entering the market; cocktails of recombinant antibodies and Fab fragments of IgG, highly affinity to epitopes of toxins, etc.

These drugs are being replaced by drugs obtained from human and animal blood plasma.

Therefore, in the coming years in Russia it is necessary to create a fundamentally new system for assessing the quality, effectiveness and safety of blood products, taking into account the further direction of their development

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