VOLGOGRAD STATE MEDICAL UNIVERSITY

DEPARTMENT OF PHARMACOLOGY AND BIOINFORMATICS

Methodological recommendations for students for practical classes
«Immunobiological and gene therapy drugs»

Thematic block: **Immunobiological drugs**

Class topic:
Preclinical development of gene therapy drugs. Regulatory documents. Strategy. Experimental models. Potential risks when using gene therapy drugs. Toxicity

Pharmaceutical faculty

1. Class aims

• teach students to analyze the stages of preclinical development of gene therapy drugs (GTDP);

• teach students the general principles of evaluating the effectiveness of GTDPs taking into account regulatory documents;

• teach students to evaluate potential risks when using GTDPs;

• teach students to evaluate the advantages and disadvantages of this group of immunobiological drugs;

2. TASKS:

• For the HTLP, study:
  - programs for preclinical development of HTLP;
  - advantages and disadvantages of these groups of immunobiological drugs;
  - main mechanisms of action and application in medicine.

• Study the features of development and production of the studied group of drugs.

• Study the general requirements for production, transportation and storage of HTLP, taking into account potential risks to human health and the environment.

3. THE FOLLOWING PRACTICAL SKILLS ARE PRACTISED DURING THE LESSON:

• ability to evaluate the stages of development of drugs of the studied group based on their mechanism of action, methods of application;

• ability to analyze the possibilities of using HTLD;

• ability to analyze the advantages and disadvantages of using HTLD and potential risks to human health and the environment.

4. ORDER OF CONDUCTING CLASSES:

Venue: classroom of the Department of Pharmacology and Bioinformatics.

Time: 2 AH

Competencies to be developed: УК-1.1.3, УК-1.2.1, УК-1.2.2, УК-1.2.3., УК-1.3.1, УК-1.3.2., УК-6.1.1., УК-6.2.1, УК-6.2.2, УК-6.3.1, УК-6.3.2, УК-6.3.3, УК-6.3.4, ОПК-1.1.1., ОПК-1.2.1, ОПК-1.2.2., ОПК-1.3.1, ОПК-6.1.1, ОПК-6.2.1, ОПК-6.3.1, ПК-7.1.1, ПК-7.2.1, ПК-7.3.1.

4.1 Technological map of the lesson

Part	№	Class stage	Time
1	1	Checking the students present at the lesson, lesson mode, lesson topic.	5 min
	2	Checking the initial level of students' knowledge (written survey).	10 min
	3	Survey on the topic of the lesson.	45 min
	4	Independent work of students (on prescriptions with analysis of the most complex prescriptions (if any in the topic), analysis of errors in medical prescriptions written by students; work with synonyms).	15 min
	5	Checking independent work	5 min
	6	Summing up the lesson. Assignment for the next lesson.	5 min
	7	Cleaning of workplaces.	5 min

4.2 Demonstrations

1. Demonstration of advertising brochures on this topic during a survey on the topic of the lesson.

4.3 **Lesson plan**

4.3.1 Introductory remarks by the teacher.

The world pharmaceutical market currently offers GM drugs containing a sequence of recombinant nucleic acids or a genetically modified microorganism or virus, although their number is still small. Among the registered gene therapy drugs for stimulating angiogenesis, one can note "Neovasculgen" (PJSC "Human Stem Cell Institute", Russia), which is a plasmid encoding VEGF165, and "Collategene" (AnGes, Ink., Japan), a plasmid with the HGF gene, which received conditional approval in Japan. Clinical trials of the drug "Corvian" - an original development of the NMIC Cardiology (Russia), which is a pDNA encoding VEGF165, as well as the drug "Yupikor" (NMIC Cardiology, Russia) - a drug with the gene of urokinase plasminogen activator (uPa) are being conducted.

At the moment, at the stage of preclinical studies, it is advisable to use current international recommendations for studying the safety of HTLD. Certain special risks of HTLD and the main requirements for preclinical safety assessment, identified possible options for optimizing the program and design of preclinical studies and established criteria for expert evaluation of the results of preclinical studies of HTLD will allow HTLD developers to rationalize the planning of preclinical studies and improve the quality of the preclinical summary for submitting documents to an expert institution for the purpose of conducting clinical studies or registering HTLD.

All types of preclinical studies of HTLD differ significantly from studies of other types of drugs. The differences include studies of specific activity, pharmacokinetics and general toxicity, which are recommended to be combined. Studies of the pharmacokinetics of HTLD replace biodistribution studies. The preclinical safety study program for HTLD, as for other biological drugs, includes mandatory studies of general toxicity and local irritant effects, pharmacological safety and immunogenicity. The duration of studies of general toxicity is usually longer than for other biological drugs, since it is determined by the duration of transgene expression and can be a long period (25-30 years). The need for reproductive toxicity studies is determined by the availability of scientific literature data on the risk of vertical gene transfer. Standard studies of immunotoxicity, genotoxicity and carcinogenicity are necessary. However, the use of HTLD may be associated with the above risks, which may require additional studies of immunotoxicity

and studies of vector DNA integration. For a HTLD, it is necessary to carefully assess the environmental safety, which concerns the health of people in contact and not in contact with the patient, as well as animals. The nature of the vector and gene, the features of the mechanism of action of the HTLD, the patient population, the results of drug isolation studies and the oncogenic potential together determine the environmental risk and significantly affect the assessment of the ratio of the expected benefit to the possible risk of using the HTLD under development. When preparing a set of documents in order to obtain permission to conduct a clinical trial or register a drug, the developer of the HTLD is required to provide a detailed scientifically substantiated position on the choice of the preclinical study program, the relevance of the animal model and key points of the study design: duration of drug administration and recovery period, dosing regimen, methods used, laboratory test systems, etc. Particular attention should be paid to a detailed justification of the absence of remote risks after the administration of the HTLD, such as off-target integration, unwanted cell mutations and oncogenic potential, vertical gene transfer, and environmental risk. As experience in development, production, preclinical and clinical studies and application of HTLDs is accumulated, the risks associated with them are revised and new safety data are obtained, which requires a dynamic and timely update of existing requirements for preclinical studies of HTLD safety. The program for preclinical studies of HTLD safety includes studies of general toxic and local irritant effects, reproductive toxicity, immunogenicity, pharmacological safety, and also takes into account the specific risks of this class of drugs. These include remote risks of using HTLDs: off-target integration, unwanted mutations and oncogenic potential, environmental risk / hazard to the environment. In this regard, an approach based on risk analysis is determined to determine the scope of necessary information and requirements for preclinical study of HTLP.
The importance of the topic in the system of training and activities of a pharmacist:
• informing the population about the advantages and disadvantages of using state-of-the-art pharmaceutical products;
• draw the attention of pharmacists to the prohibition of dispensing drugs by pharmacies (clause 5, 6 of the RF Government Resolution of 22.12.2011 No. 1081 "On licensing pharmaceutical activities")

- ✓ Optimization of the preclinical development program of HTLP.

Preclinical studies of the safety of HTLP may be combined with biodistribution studies (distribution, persistence and clearance). For example, the study of the general toxicity of Cerepro was combined with a study of specific activity and a study of the biodistribution of the drug, which is also acceptable. With this approach, the disease model must be highly specialized and validated, and the combined studies of specific activity and biodistribution must be carried out in compliance with the principles of Good Laboratory Practice (GLP). Such a study is possible if it allows for a clear identification of the toxic effect of HTLP and the manifestations of the disease, which also makes it possible to assess the safety of the drug against the background of the disease. An example is the drug Advexin, the developers of which were recommended to study the design on model systems with a deficiency of the p53 gene, which corresponded to the situation in patients with Li-Fraumeni syndrome and could allow for the

interpretation of the depletion of lymphocytes and necrosis of individual cells found in animals.

- ✓ Selection of tissues to be studied.

In a biodistribution study, it is recommended to analyze a set of organs and tissues/biological fluids, including the brain, spinal cord (cervical, thoracic and lumbar regions), liver, kidneys, lungs, heart, spleen, adrenal glands, gonads, tissues at the injection site and blood, which can only be reduced in the absence of systemic exposure to the HTLP. When using different animal species in specific activity and toxicity studies, it is recommended to study the biodistribution of the HTLP in all species used to understand species-specific differences, the impact of the disease, and to properly extrapolate the data to humans. Toxic effects detected in toxicology studies should be interpreted both in relation to the entire gene therapy construct (i.e., the HTLP) and in relation to the expression products.

- ✓ Duration of general toxicity studies.

Many HTLDs are intended for a single therapeutic use followed by long-term, multi-year expression of the transgene, which is a significant advantage over existing replacement therapies with multiple uses. The duration of general toxicity studies of such drugs, namely the period from drug administration to the planned euthanasia of animals, reflects the expected duration of transgene expression in humans and also includes the recovery period.
Thus, for HTLDs intended for single administration in clinical settings, it is acceptable to conduct a toxicology study with a single administration but an extended observation period. Specific activity studies provide information on the duration and magnitude of transgene expression, and biodistribution studies provide information on the pharmacokinetics of the drug in the experimental animal species (vector persistence, as well as clearance and mobilization). The duration of the biodistribution study is determined by the time interval until the detectable signal completely disappears or until a long-term plateau of the positive signal is reached. The second most important and controversial point is the timing of endpoint assessment and the associated number of experimental animals in groups. It is recommended to include intermediate groups of animals in toxicology studies to assess toxicity parameters at peak biodistribution values. For example, for an AAV vector, these are changes associated with the initial peak of transgene expression (after 4 weeks) and steady-state exposure to the transgene (after 13 weeks), which require euthanasia of animals. Monitoring of acute effects of the interaction of the viral vector with the test system is also required, which can be done by assessing the clinical condition of the animals and intravital clinical and laboratory data. If there is a limited amount of data on the animal species used for studies of this type of HTLD, an intact control group should also be included in the study.

- ✓ Dosage route and regimen.

The design of biodistribution and toxicology studies of a new HTLD should reflect the conditions of clinical use. It is permissible to use in experiments a route of administration that ensures greater distribution of the drug in animals than in clinical use. For example, the preclinical studies of Advexin used the intravenous route of administration, whereas in the clinical setting it is administered intratumorally and subcutaneously, limited distribution has

been demonstrated. In contrast, in the biodistribution studies of Glybera, more drug was found in the testes and epididymis following intramuscular administration compared to intravenous administration. This suggests that although the intravenous route is generally considered to create a worst-case scenario, in biodistribution studies this should be confirmed or refuted. The regimen of administration of the HTLD in preclinical studies should be as close as possible to the conditions of clinical use. On the other hand, repeated dose toxicity studies should be envisaged if long-term persistence of vector DNA is expected and the vector kinetics in the experimental animal do not correspond to those in humans or if multiple administration of the HTLD to patients is planned.

- ✓ Control groups.

Interpretation of the results of the biodistribution and general toxicity study of HTLD based on a viral vector is often based on the analysis of the current scientific literature on previously obtained preclinical/clinical data on a similar viral vector, and it is quite rare to need to use a vector without a transgene or containing a non-functional transgene as a control group in studies. On the contrary, for HTLD containing non-viral vectors, it is advisable to conduct biodistribution and safety studies by including in the experiment a group of animals receiving this vector without a transgene, given, as a rule, a small amount of available literature data on the safety of such constructs36.

- ✓ Study doses.

The doses of the drug for preclinical studies should be adjusted taking into account the characteristics of the animal model used, while ensuring the determination of the breadth of the therapeutic effect of the drug. A feature of the HTLD is the use of the drug in an initial dose corresponding to the minimum effective dose already during the first use in humans. This approach is based on the principles of ethics and is associated with the development of neutralizing antibodies that prevent repeated administration of the HTLD. The use of the HTLD in the minimum effective dose is permissible taking into account the medical need, the shortage of approved treatments for certain diseases and the narrow time window for the use of the HTLD. The studied doses should reveal clinically significant toxic effects and all potential target organs. For example, in a preclinical study in piglets and non-human primates where supraphysiological expression of the human SMN transgene was achieved, proprioception and ataxia were observed after intravenous administration of neurotropic AAV serotypes, which was associated with high transduction of dorsal root ganglia and subsequent toxicity. The data from these and other studies demonstrate that, despite the accumulated volume of information, further evaluation of appropriate routes of administration and doses of HTLD, choice of capsid, and vector genome design to achieve tissue or cell specificity are still needed even for approved drugs.

- ✓ Laboratory test systems.

The sensitivity of the method must be taken into account when planning studies and interpreting results. Analysis of vector DNA and the transgene product (mRNA or protein) is critical to assess the efficacy and safety of the HTLD under development. The nucleotide sequence

analysis methods used must be highly sensitive, specific, and validated. The priority methods are quantitative real-time polymerase chain reaction (qPCR) for DNA and reverse transcription-PCR (RT-qPCR) for RNA39. Other methods may be used if sufficiently justified.

- ✓ Relevance.

Of particular importance is the relevance of the experimental model. It is recommended that the same animal model be used in the toxicity study as in the specific activity study. Nevertheless, the choice of relevant animals for preclinical studies of the developed GTLP should be thoroughly justified by the developer in the registration dossier materials and be based on the similarity between the experimental animal species and humans according to the following key criteria: transduction, infectious ability of the vector to replicate in tissues, tissue distribution and expression of cellular receptors of the vector (selectivity, isolation), activity of regulatory elements (promoters, enhancers, etc.), homology and biological response to the transgene product, permissible volume for administration to animals, and other pharmacokinetic features (in particular, metabolism). The use of large animals as a second experimental species is justified by their greater biological and physiological similarity to humans. Research only on a large animal species is sometimes associated with a small sample size, which can be partly compensated for by increasing the frequency and duration of observation.

- ✓ Study doses.

The doses of the drug for preclinical studies should be adjusted taking into account the characteristics of the animal model used, while ensuring the determination of the breadth of the therapeutic effect of the drug. A feature of the HTLD is the use of the drug in an initial dose corresponding to the minimum effective dose already during the first use in humans. This approach is based on the principles of ethics and is associated with the development of neutralizing antibodies that prevent repeated administration of the HTLD. The use of the HTLD in the minimum effective dose is permissible taking into account the medical need, the shortage of approved treatments for certain diseases and the narrow time window for the use of the HTLD. The studied doses should reveal clinically significant toxic effects and all potential target organs. For example, in a preclinical study in piglets and non-human primates where supraphysiological expression of the human SMN transgene was achieved, proprioception and ataxia were observed after intravenous administration of neurotropic AAV serotypes, which was associated with high transduction of dorsal root ganglia and subsequent toxicity. The data from these and other studies demonstrate that, despite the accumulated volume of information, further evaluation of appropriate routes of administration and doses of HTLD, choice of capsid, and vector genome design to achieve tissue or cell specificity are still needed even for approved drugs.

- ✓ Laboratory test systems.

The sensitivity of the method must be taken into account when planning studies and interpreting results. Analysis of vector DNA and the transgene product (mRNA or protein) is critical to assess the efficacy and safety of the HTLD under development. The nucleotide sequence analysis methods used must be highly sensitive, specific, and validated. The priority methods are

quantitative real-time polymerase chain reaction (qPCR) for DNA and reverse transcription-PCR (RT-qPCR) for RNA39. Other methods may be used if sufficiently justified.

- ✓ Relevance.

Of particular importance is the relevance of the experimental model. It is recommended that the same animal model be used in the toxicity study as in the specific activity study. Nevertheless, the choice of relevant animals for preclinical studies of the developed GTLP should be thoroughly justified by the developer in the registration dossier materials and be based on the similarity between the experimental animal species and humans according to the following key criteria: transduction, infectious ability of the vector to replicate in tissues, tissue distribution and expression of cellular receptors of the vector (selectivity, isolation), activity of regulatory elements (promoters, enhancers, etc.), homology and biological response to the transgene product, permissible volume for administration to animals, and other pharmacokinetic features (in particular, metabolism). The use of large animals as a second experimental species is justified by their greater biological and physiological similarity to humans. Research only on a large animal species is sometimes associated with a small sample size, which can be partly compensated for by increasing the frequency and duration of observation.

 Circulating antibodies significantly impair the ability of vectors to transduce target cells and weaken the resulting adaptive immune responses;

 Genome editing technologies may also be associated with the risk of immunogenicity;

 Immunogenicity is also one of the potential problems when using non-viral vectors;

 Liposomes non-specifically bind to serum proteins and cause cell damage along with activation of the immune system.

Thus, when developing a HTLP for multiple use, it is necessary to assess its immunogenicity (the formation of an anti-vector immune response). At the stage of preclinical studies of HTLP, it is necessary to assess the risk of developing immunological reactions in humans (if conditions allow, such endpoints can be included in general toxicity studies on animals, for example, the occurrence of immunotoxicity, multiple organ inflammation, deposition of immune complexes in internal organs, cytokine storm, etc.). Particular attention should be paid to the risk of cross-reactivity and background autoimmune reactions. It is important to remember that the target population of HTLP is often young children with an immature immune system. In this regard, when conducting preclinical toxicity studies using immature animals, a situation may arise when animals do not form antibodies, while antibody formation is expected.

 Local irritant effect. Evaluation of the increase in the frequency and severity of inflammatory infiltration and myodegeneration at the site of administration of HTLP drugs.

 Modifications to the manufacturing process.

Any modification of the HTLP nucleic acid sequence has the potential to affect the safety of the final product and requires additional safety assessment and/or intermediate/bridging experimental data. Additional studies related to long-term risks

The specific properties of HTLD may create safety issues such as insertional mutagenesis, ectopic or unregulated transgene expression, long-term persistence and off-target dissemination that do not occur with other drugs, including biologicals. Therefore, in some cases, additional

preclinical studies are required.
Vector DNA integration and oncogenic potential. Undesirable integration of vector DNA into the host cell genome can lead to insertional mutagenesis, one of the consequences of which is oncogenicity. The first trials of HTLD based on viral vectors showed that the drugs were clinically effective, but at the same time revealed genotoxicity caused by off-target integration. In particular, the use of the first generation of gamma-retroviral vectors for the treatment of X-linked severe combined immunodeficiency (SCID) was accompanied by a high frequency (4 out of 9 patients) of T-cell leukemia.
In addition, integration has the potential to form chimeric gene fusions consisting of proviral and host sequences. Lentiviral vectors have been shown to induce aberrant splicing of cellular transcripts. Continuous efforts to improve or develop new types of retroviral vectors have significantly reduced genotoxicity, but insertional mutagenesis still remains an urgent problem. Therefore, it is recommended to study the possibility of integration before the first administration of GTL to humans to detect random integration even for those viral vectors for which it is not expected. For vectors whose nature implies the possibility of integration into the target cell genome, it is necessary to identify the tissues in which integration occurs (target and off-target), the number of copies and the sites of integration of vector copies into the genome (in vitro or in vivo), the structural integrity of the integrated vector, its genomic stability.
Vertical gene transfer.
Standard reproductive toxicity studies of HTLDs have low predictive power, but in some cases, when there are gaps in the available information, such studies may be useful. For example, a study of the embryofetal toxicity of the drug was conducted for Imlygic and demonstrated the ability to cross the placental barrier without affecting embryofetal development. In addition, if necessary, preclinical studies should be conducted to assess the possibility of unintentional transmission of gene transfer vectors along the germline and the possibility of virus excretion (namely, virus excretion with sperm) even before the first use of the drug in humans.
Promising areas of development of HTLDs include expanding the patient population to pregnant women, for the treatment of whom doctors have a small arsenal of therapeutic agents, as well as the use of drugs for the intrauterine treatment of a developing embryo/fetus with a genetic disease. Thus, it is possible to treat neurodegenerative monogenic diseases for which existing drugs are unable to cross the blood-brain barrier. Some serotypes of AAV gene delivery vectors have been experimentally confirmed to be able to penetrate the blood-brain and placental barriers after intravenous administration. Embryofetal and perinatal toxicity studies may be required for development of drugs for intrauterine treatment to study the effects on the fetus, for example, of placental transfer of locally produced cytokines.

- ✓ Environmental risk.

The main potential risks to human health are associated with the release of vector particles into the environment, the formation of recombinant viruses during production or after infusion of HTLP, and insertional mutagenesis. Risks associated with the release of vector particles include unintended exposure of HTLP to humans for whom the drug is not intended, with overexpression of the normal human protein and induction of an immune response against the vector particles. A

similar risk is relevant for animals. Based on this, to predict the risks of using HTLP and to plan clinical trials, it is necessary to conduct studies of the drug excretion with secretions and physiological fluids (including saliva, tears, sweat). Quantitative assessment by PCR is preferable.

The toxic effects of non-viral vectors are also determined by the non-biodegradable nature of some of these compounds (primarily inorganic ones), which is an additional obstacle to their clinical use. A serious problem with non-degradable inorganic nanoparticles is their potential accumulation in the body. Nanoparticles smaller than ~6 nm can be filtered by glomerular filtration in the kidneys and excreted from the body with urine, and larger nanoparticles, especially with a significant surface charge, can accumulate in tissues for a long time.

4.3.2 Analysis of theoretical material.

4.3.3 Conducting the test

4.3.5. Independent work of students:

1. Conduct a search and write down the names of immunobiological medicinal products related to the GTP.
2. Fill in the table “Program of preclinical safety studies required for state registration of various types of medicinal products in the Russian Federation and the EU”. The information is entered into the students’ workbooks.

4.3.6 Checking the students’ independent work.

4.3.7 Summing up the lesson. Answering students’ questions.

4.3.8 Concluding remarks by the teacher.

Составитель,
профессор, д.б.н. М.П. Воронкова

Приложение 1

Перечень рекомендуемой литературы, включая электронные учебные издания:

1. Харкевич Д. А. Фармакология : учебник / Харкевич Д. А. - 11-е изд., испр. и доп. - М. : ГЭОТАР-Медиа, 2015. - 755, [5] с. : ил. - Текст: непосредственный.
2. Харкевич, Д. А. Фармакология : учебник / Д. А. Харкевич. - 13-е изд. , перераб. - Москва : ГЭОТАР-Медиа, 2022. - 752 с. : ил. - ISBN 978-5-9704-6820-3. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970468203.html
3. Фармакология : учебник / под ред. Р. Н. Аляутдина. - 6-е изд. , перераб. и доп. - Москва : ГЭОТАР-Медиа, 2022. - 1104 с. - ISBN 978-5-9704-6819-7. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970468197.html
4. Майский, В. В. Фармакология с общей рецептурой : учебное пособие / В. В. Майский, Р. Н. Аляутдин. - 3-е изд. , доп. и перераб. - Москва : ГЭОТАР-Медиа, 2017. - 240 с. - ISBN 978-5-9704-4132-9. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970441329.html
5. Аляутдин, Р. Н. Фармакология. Ultra light : учеб. пособие / Р. Н. Аляутдин. - Москва : ГЭОТАР-Медиа, 2012. - 584 с. - ISBN 978-5-9704-1985-4. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970419854.html
6. Онкология : учебник / М. И. Давыдов, Ш. Х. Ганцев [и др.]. - Москва : ГЭОТАР Медиа, 2020. - 920 с. : ил. - ISBN 978-5-9704-5616-3. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970456163.html
7. Онкология : учебник / под ред. С. Б. Петерсона. - 2-е изд. , перераб. и доп. - Москва : ГЭОТАРМедиа, 2018. - 288 с. : ил. - ISBN 978-5-9704-4704-8. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970447048.html
8. Онкология / под ред. Чиссова В. И. , Давыдова М. И. - Москва : ГЭОТАР-Медиа, 2014. - 1072 с. - ISBN 978-5-9704-3284-6. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970432846.html
9. Медицинская микробиология, вирусология и иммунология : Т. 1 : учебник / под ред. Зверева В. В. , Бойченко М. Н. - Москва : ГЭОТАР-Медиа, 2020. - 448 с. - ISBN 978-5-9704-5835-8. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970458358.html
10. Медицинская микробиология, вирусология и иммунология : Т. 2 : учебник / под ред. Зверева В. В. , Бойченко М. Н. - Москва : ГЭОТАР-Медиа, 2021. - 472 с. - ISBN 978-5-9704-5836-5. - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : https://www.studentlibrary.ru/book/ISBN9785970458365.html
11. Этиотропная терапия острых вирусных инфекций у детей : учеб. пособие для спец. 06010365 "Педиатрия" / Крамарь Л. В., Арова А. А., Желудков Ю. А. и др. - Волгоград : Изд-во ВолгГМУ, 2012. - 156 с. - Текст: непосредственный.
12. Иоанниди Е. А. Хронические вирусные гепатиты B, D и C : этиопатогенез, эпидемиология, клиника, лечение и профилактика : учеб. пособие / Иоанниди Е. А., Божко В. Г., Беликова Е. А., Александров О. В. ; ВолгГМУ Минздрава РФ. - Волгоград : Изд-во ВолгГМУ, 2016. - 71, [1] с. : табл. - Текст : электронный // ЭБС ВолгГМУ : электронно-библиотечная система. - URL: http://library.volgmed.ru/Marc/MObjectDown.asp?MacroName=%D5%F0%EE%ED%E8%F7_%E2%E8%F0%F3%F1_%E3%E5%EF%E0%F2%E8%F2%FB_2016&MacroAcc=A&DbVal=47

13. Kharkevitch D.A., Pharmacology / Kharkevitch D.A. - M. : ГЭОТАР-Медиа, 2008. - 672 с. - ISBN 5-9704-0264-8 - Текст : электронный // ЭБС "Консультант студента" : [сайт]. - URL : http://www.studentlibrary.ru/book/ISBN5970402648.html (дата обращения: 28.02.2020). - Режим доступа : по подписке.

Перечень профессиональных баз данных, информационных справочных систем, электронных образовательных ресурсов, рекомендуемых для подготовки:

1. http://vrachirf.ru/ - Информационный портал Врачи России
2. https://pharmarf.ru – информационный портал Фарма России
3. https://www.rlsnet.ru/ - РЛС (регистр лекарственных средств России) (информационная справочная система)
4. http://www.drugs.com - Информационная база о лекарственных препаратах (информационная справочная система)
5. https://grls.pharm-portal.ru/ - государственный реестр лекарственных средств.
6. http://elibrary.ru – Электронная база, электронных версий периодических изданий на платформе Elibrary.ru (профессиональная база данных)
7. http://www.consultant.ru/ – Справочно-правовая система «Консультант-Плюс» (профессиональная база данных)