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Genetic Research Application in the Study of Pharmaceuticals

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Abstract: The current science and research trends, as well as the development of personalized medicine, point to the need to use genetic tests in course of the study of pharmaceuticals. Pharmacogenetic testing has become indispensable when developing new pharmaceuticals in order to study both the peculiarities of pharmacodynamic effects or the prospects of personalized treatment, and the characteristics of metabolism or drug-drug interaction. In addition, the introduction of pharmacogenetics in bioequivalence studies allows limiting, at early stages, the criteria for inclusion or non-inclusion of volunteers based on certain gene polymorphisms determining the metabolic rate.

The study of the genetic characteristics of clinical trial participants allows a more detailed analysis of the role of gene polymorphisms in terms of both pharmacokinetics and pharmacodynamics of the studied pharmaceuticals.

A separate important issue is genetic material collection from the clinical trial participants. On the one hand, the use of biological material collections is an essential tool for accomplishing the practical tasks in both the pharmaceutical industry and the state-of-the-art medicine. On the other hand, the legal review and ethics review of genetic material collection and use can become formidable barriers to the development

of biobanking. The existing legislative differences between Russia and other countries allow identifying the most challenging regulatory aspects, and can contribute to international law harmonization in the sphere of biobanking in the future.

Keywords: pharmacogenetics, biobanking, clinical studies [clinical trials], ethics review, law, legislation, genetic material

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I. Background

The current science and research trends, as well as the development of personalized medicine, point to the need to use genetic tests in course of the study of pharmaceuticals. Pharmacogenetic testing has become absolutely indispensable when developing new pharmaceuticals in order to study both the peculiarities of pharmacodynamic effects or the prospects of personalized treatment, and the peculiarities of metabolism or drug-drug interaction. In addition, the introduction of

pharmacogenetics in bioequivalence studies allows limiting, at early stages, the criteria for inclusion or non-inclusion of volunteers based on certain gene polymorphisms determining the metabolic rate. However, genetic material circulation in clinical studies/trials remains a subject of heated debate, both ethically and legally.

II. Pharmacogenetics in clinical studies

One of the key ways of improving the efficacy and safety of pharmacotherapy is the introduction of personalized (personified) medicine into the clinical practice. It is based on an individual approach to the choice of pharmaceuticals/drugs and the dosage regimen taking into account the factors influencing the pharmacological response of a particular patient (Kukes and Bochkov, 2007).

Currently, there are various points of view on the need for pharmacogenetic testing in clinical studies. Pharmacogenetic testing has become absolutely indispensable when developing new pharmaceuticals in order to study both the peculiarities of pharmacodynamic effects or the prospects of personalized treatment, and the peculiarities of metabolism or drug-drug interaction. The introduction of pharmacogenetics in bioequivalence studies allows limiting, at early stages, the criteria for inclusion or non-inclusion of volunteers based on certain gene polymorphisms determining the metabolic rate. This approach may reduce the number of study/trial participants. However, in crossover design conditions, the same subjects take part in both phases of the study (of the tested and the reference pharmaceutical), and their pharmacogenetic peculiarities do not change in these phases, and, therefore, the individual features have little effect on bioequivalence results. In this connection, the pharmacogenetic approaches to clinical studies/trials require special consideration, as they are directly related to the peculiarities of pharmacokinetics and the results of bioanalysis.

Interindividual differences in the pharmacological response can be explained by various factors: gender, age, bad habits, the functional state of organs and systems (primarily the gastrointestinal tract (GIT), liver, kidneys, and blood), the state and the etiology of the underlying disease, concomitant therapy, as well as the patient's genetic peculiarities, etc.

More often than not, the cause of undesirable (adverse) reactions of a human body to pharmaceuticals lies in the genetic characteristics (Karpenko, 2007). The study of the patients' genetic characteristics (peculiarities) formed the foundation for the development of pharmacogenetics and, later, personalized medicine.

All the stages of drug pharmacokinetics (absorption, distribution, metabolism/biotransformation, excretion) are regulated accordingly, therefore the polymorphisms of various genes can influence all of the aforementioned pharmacokinetic processes.

Identification of the patients' genetic characteristics (peculiarities) allows forecasting the pharmacological response to a drug/pharmaceutical, and, thus, increasing the efficacy and safety of its application, since the identification of the corresponding allelic variant leading to changes in the patient's pharmacokinetics and/or pharmacodynamics requires correction of the therapy (the dose of the pharmaceutical, as well as the frequency and the route of administration, or the need to replace it with another pharmaceutical). In other words, the use of this approach in clinical practice allows optimizing pharmacotherapy (Khokhlov et al, 2017).

Currently, the highest clinical importance is attributed to the gene polymorphisms which control the synthesis and the operation of the enzymes involved in biotransformation of pharmaceuticals, as well as transport proteins (transporters) involved in the processes of absorption, distribution and excretion of pharmaceuticals. For example, genetic polymorphism is characteristic of the genes encoding the enzymes for phase I metabolism, mainly Cytochrome P450 isozymes, and of the transporters, mainly P-glycoprotein (Avdeev, 2010).

The introduction of a personalized approach to treatment of various internal organ diseases into the medical practice is aimed at increasing both the efficacy of treatment and the safety of pharmacotherapy (Khokhlov, 2012). This is of special importance for a broad range of pharmaceuticals, such as anticoagulants, psychotropic medications, proton-pump inhibitors, as well as some pharmaceuticals for treatment of cardiac ischemia and hypertension (Morozova, 2016).

It is known that about 60 % of drug oxidization involves CYP3A4 enzyme system. CYP3A4 system, being the basic one in the human body,

is characterized by individual activity, and also by unimodal distribution in the population and absence of genetic polymorphism (Borodulin, 2011).

Interindividual differences in the rate of drug metabolism allow identifying groups of patients with different types of activity of certain isoenzymes.

"Extensive" metabolizers (extensive metabolism, EM) are individuals with a "normal" rate of metabolism of certain drugs, as a rule, homozygous for the "wild-type" allele of the corresponding enzyme gene. The majority of people are extensive metabolizers.

"Poor" metabolizers (poor metabolism, PM) are individuals with a low rate of metabolism of certain drugs, as a rule, homozygous (in case of autosomal recessive inheritance) or heterozygous (in case of autosomal dominant inheritance) for the "slow" allele of the corresponding enzyme gene. The characteristic feature of such patients is synthesis of a "deficient enzyme", or a total absence metabolic enzyme synthesis, which results in a decreased, or even zero, enzyme activity. Pharmaceuticals accumulate in high concentrations in the bodies of poor metabolizers, resulting in pronounced ADRs. Therefore, the drugs for poor metabolizers need to be dosed very carefully: the dose should be lower than that for extensive metabolizers.

"Ultra extensive" or "ultra rapid" metabolizers (ultra extensive metabolism, UM) are individuals with a high rate of metabolism of certain drugs, as a rule, homozygous (in case of autosomal recessive inheritance) or heterozygous (in case of autosomal dominant inheritance) for the "rapid/fast" allele of the corresponding enzyme gene. As a consequence, drug concentration in blood turns out to be insufficient to achieve a therapeutic effect. Therefore, the drug dose for ultra extensive metabolizers should be higher than for extensive metabolizers (Sychev et al., 2011).

In addition to cytochrome P450 isoenzymes, an important role in drug pharmacokinetics is played by P-glycoprotein, MRP, OATP, OST, and MATE. In the intestinal epithelium, P-glycoprotein provides the efflux of medication/drug (its substrate) into the intestinal lumen, thereby reducing the absorption thereof. In hepatocytes and renal epithelium, it mediates excretion of xenobiotics into the lumens of bile capillaries and renal tubules, respectively, and also provides impermeability of histohematogenous barriers to lipophilic substances (Ernest and Bello-

Reuss, 1998). Currently, the most studied polymorphism is the one associated with a change in the functioning of P-glycoprotein: it is a "silent" (i.e., not resulting in amino acid substitution) single-nucleotide substitution in exon 26 at position 3435 (C3435T), cytosine nucleotide substitution for thymine nucleotide in the promoter region of ABCB1 gene (formerly called MDR1), the gene encoding the P-glycoprotein synthesis (Yakusheva, 2011). It has been proved that, in homozygotes for the CC allele, the ABCB1 gene expression in the small intestine was more than twice higher than the expression in homozygotes for the TT allele, which indicated a higher activity of P-glycoprotein in CC genotype individuals. This is another proof of the need to study the ABCB1 genetic polymorphism with the purpose of pharmacotherapy individualization.

P-glycoprotein performs many various functions. The available data show that this protein functions as a body protector minimizing gastrointestinal absorption of xenobiotics and toxins, and stimulating the excretion thereof by the liver and kidneys (Andersen et al., 2009). It also takes part in aldosterone and cortisol secretion by the adrenal glands, and limits the penetration of glucocorticosteroids into the brain through the blood-brain barrier. Finally, it significantly contributes to the regulation of apoptosis, which is especially important in the treatment of malignant tumors, as one of the expected effects of chemotherapy is the activation of autogenous programmed death of mutated cells.

The biochemical compounds interacting with P-glycoprotein can be divided into P-glycoprotein substrates and P-glycoprotein inhibitors. The study of the ability of pharmaceuticals to suppress or enhance the P-glycoprotein function is of high practical importance, since these features can change the pharmacokinetics and bioavailability of pharmaceuticals when co-used, and lead to development of toxic effects of these pharmaceuticals, or, conversely, to a decrease in the concentration of substrates in blood and, as a consequence, to a decrease in their therapeutic activity (effect) (Collet et al., 2009).

Depending on various conditions, the same pharmaceuticals can act both as substrates and inhibitors for P-glycoprotein. For example, verapamil acts as a substrate of P-glycoprotein in small concentrations, but when the dose is increased, it exhibits the properties of an inhibitor of P-glycoprotein (Ramenskaya et al., 2007).

Bioequivalence studies are accumulating more and more data on the link (association) between polymorphisms of various genes and the individual pharmacokinetics, pharmacodynamics, efficacy, and safety of various pharmaceuticals. Thus, the pharmacogenetic testing results serve as a criterion for inclusion or non-inclusion of a volunteer into the study. But in that case, if it comes to registration of a pharmaceutical, the pharmacogenetic testing results will appear in the directions for drug use (medical application). A promising option is to use pharmacogenetic testing for biotransformation enzymes when selecting the volunteers for bioequivalence studies, which allows excluding "poor" or "ultra extensive" metabolizers, thereby reducing the coefficient of variation of pharmacokinetic parameters, and, hence, the number of volunteers required for participation, which might reduce the overall cost of the study (Sychev, 2016).

Since the emergence of the ideas about the genetic nature of pharmaceutical response variability, and over the next several decades, the system of clinical studies of pharmaceuticals and pharmacogenetics have evolved independently, without common points of contact. However, a number of recent research publications, as well as the development of the corresponding recommendations and guidelines, are evidencing the start of interaction. Perhaps, soon it will be impossible to perform a clinical study/trial (CT) without genetic information. The use of pharmacogenetic information in CTs can become widespread, since it does not require to develop a complex algorithm for interpreting the data generated during genetic testing. The point is that the objectives of personalized therapy differ from those of CTs: to predict the probability of side effects or the efficacy of treatment for a particular patient who is different from other individuals in many respects (e.g., in the predisposition to the development of certain side effects) is one thing, and to select CT participants with certain similar genetic features is quite another. However, after confirmation of the efficacy and safety of the studied pharmaceutical, the phase of larger-scale clinical trials with the involvement of a broader range of people begins. Here comes the question of whether the extent of the pharmaceutical activity (effect) will be the same, and whether it will be as safe for genetically diverse population of patients. To answer this question, additional studies/trials are required with the incorporation of

knowledge and experience of pharmacogenetics into CTs. Such studies do not necessarily generate an algorithm for taking into account genetic factors in doctor's prescriptions, but the very fact of such studies should ensure the safety of genetically diverse people. This means that the researchers should have a thorough understanding of metabolism and the action/effect of the studied pharmaceutical, and know what genetic factors may influence the pharmacological response (Khokhlov et al., 2017).

It is known that the genetics of model animals is of high importance at the preclinical trial stage. As a rule, genetically uniform inbred lines obtained through multiple mating of closely related specimen are used for that. Certainly, confirming the efficacy of a new pharmaceutical for humans during phase II CT with a limited number of volunteers is usually possible only with careful selection of the CT participants. Selection of the patients with a similar response [susceptibility] to the tested pharmaceutical it no less important than the "external" features (age, height, body mass index, etc.). Inclusion of genetic factors in the CT participant selection criteria will help to reduce the level of interindividual variability of the pharmacological response, making it possible to obtain more comprehensive information about drug effectiveness and safety using a small sample. For each drug/pharmaceutical, the "set" of identified genes will depend on the peculiarities of metabolism, the ways of excretion and the mechanism of action of the pharmaceutical, but the range of polymorphisms basically coincides with the list of genetic markers for which the evidence base was collected in course of pharmacogenetic studies. Among them, the polymorphism of the genes of cytochrome P450 isoenzymes, UDP-glucuronosyltransferases, N-acetyltransferase 2, some methyltransferases, drug transporters (P-glycoprotein, etc.) is of high importance. Attention should also be paid to the genes encoding the target molecules (receptors, enzymes, ion channels) of the pharmaceutical, and the proteins involved in certain pathological processes (blood clotting factors, apolipoproteins, HLA system genes, etc.) against which the tested pharmaceutical should act. State-of-the-art genetic testing is fast, reliable and valid for a lifetime. It is known that pharmacokinetic processes are more predictable than pharmacodynamic ones; therefore, pharmacogenetic tests allowing prediction of pharmacokinetics are used in clinical practice more often. First, it is easily determined and/or verified

by direct quantitative measurements. Second, the changes in enzyme activity, as a rule, affect several substrates in a similar way. Identification of the allelic variants well-known to researchers (e.g., CYP2C9*2, CYP2C9*3, CYP2C19*17, CYP2D6*4, etc.) can be used to study many substrates.

Genetic testing can also be supplemented with pharmacokinetic studies (e.g., phenotyping, which involves measuring the metabolic ratio in blood when administering the probe substrate). Study of genetic factors is practiced in many countries. In the US, the pharmacogenetic approach is regulated by the *Guidance for Industry: Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendation for Labeling* (FDA), while the European Union has adopted such guidelines as *Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling*, etc. *Guidance for Industry. E16 Biomarkers Related to Pharmaceutical or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions* has been published within the framework of conferences on harmonization (Khokhlov et al., 2017). In Russia *Recommendations for Pharmaceutical Companies on the Study of Biotransformation and Transporters of New Pharmaceuticals*, pointing out the need to take into account the genetic factors, were published in 2009 (Sychev, 2009). However, this is obviously insufficient for an active interaction between pharmacogenetic experience and clinical studies.

The US has broad experience in pharmacogenetic research and the use of the resulting information. The FDA Guidance mentions the following objectives for incorporation thereof in the CT process:

1. Identifying the basis for major individual deviations ("outliers") of pharmacokinetic processes and inter-subject variability in clinical response;

2. Excluding from clinical trials the participants with genetically induced deviations in the processes of pharmacokinetics and pharmacodynamics affecting the efficacy and safety of pharmaceuticals;

3. Estimating the magnitude of potential drug-drug interactions;

4. Investigating the molecular or mechanistic basis for the potential lack of efficacy or occurrence of adverse pharmaceutical reactions;

5. Designing clinical trials to test the effect of polymorphisms on the pharmacological response in certain subgroups (i.e., use in the population

"enrichment" strategy involving selection of the trial/study participants with a certain genotype).

The purpose of genetic testing in clinical studies/trials differs depending on the phase of the study of a new pharmaceutical. In the initial phase, participants with the most common genotype are selected (e.g., "poor" or "ultra extensive" metabolizers are not included). The final phases of clinical trials may include participants with significant genetically induced deviations in the pharmacological response.

In phases I and II of CTs, the following groups of participants are selected based on genetic features:

1. Groups of participants who should receive lower or higher doses of the studied pharmaceutical (which is usually due to the genetic differences in drug absorption, distribution, excretion, or metabolism). These trials/studies help to define the dose range for the subsequent CT phases;

2. Groups of participants who respond to therapy (this approach has become widespread in the oncologic setting);

3. Groups of participants with an increased risk of adverse drug reactions (the pharmaceuticals that cause such reactions are not acceptable if side effects cannot be predicted and/or prevented).

The EU guidelines also address a number of fundamental issues of genetic diagnostics applicability (Khokhlov et al., 2017).

It is assumed that pharmacogenetic studies assessing the pharmacokinetics of a new drug are necessary if the main metabolic pathways, or the transport of pharmacologically active drug compounds, and/or the active or toxic metabolites thereof, involve the proteins the activity of which depends on genetic polymorphisms. In order to plan the identification of genetic polymorphisms, a researcher should have a good understanding of the pharmacokinetic and pharmacodynamic processes in which the new pharmaceutical/drug is involved. When the molecular mechanisms are not known well enough, genetic approaches should be used in case of an unexplained variability in pharmacokinetic parameters. At the same time, it might become necessary to search for new pharmacogenetic factors. Gradually, as the cost of sequencing is decreasing, it is becoming possible to sequence polymorphic regions, which can be especially useful when searching for new significant polymorphisms. If unexplained changes in pharmacokinetics are detected, the samples of

the biological material containing the DNA are collected and stored for further work.

The EU documents specify that if a genotype predictably affects pharmacokinetics, efficacy and/or safety, genetic information should be involved at all CT phases. In this case, the extensive information collected can serve as a basis for development of pharmacogenetic recommendations. It is assumed that all the necessary pharmacogenetic information should be collected by the end of phase III CT. Based on the results of the trial/study, an assessment of the clinical consequences of genetic differences should be made using the statistical data.

In Russia, many international CTs are performed, including those involving collection of genetic material and pharmacogenetic testing. However, pharmacogenetic information analysis plays a secondary role, genotyping takes place on a voluntary basis, and the CT participants can refuse to take part in it while remaining included into the trial/study. In Russian CT practice, genetic information tends not to be taken into account in the initial phases, and pharmacogenetic studies usually take place in the later CT phases (which is still typical of the global practice as well).

In 2009, *Recommendations for Pharmaceutical Companies on the Study of Biotransformation and Transporters of New Pharmaceuticals: Research Design, Data Analysis and Information Entry into the Directions for Use* were published in Russia. As far as the use of genetic information is concerned, the *Recommendations* say only the following: "Identification of genetic polymorphisms of the enzymes involved in biotransformation is advisable for *in vivo* study participants when studying such cytochrome P450 isoenzymes as CYP2D6, CYP2C19, and CYP2C9" (Sokolov, 2015). The brochure *Evaluating the Bioequivalence of Pharmaceuticals — Methodology Guidelines*, that was issued around the same time, considers genotyping advisable if it is known that the studied pharmaceutical undergoes biotransformation controlled by genetically polymorphic cytochrome P450 isoenzymes (CYP2C9, CYP2C19, CYP2D6) in order to prevent participation of "poor" and "ultra extensive" metabolizers in the trial/study (the Scientific Centre for Expert Evaluation of Medicinal Products Federal Institution, 2008).

Both Russian documents (which are of a recommendatory nature) only point out the issue without any further details on the interaction between the pharmacogenetic and the clinical trials/studies. The strategies which can be applied in CTs based on genetic testing are not described either. However, the CTs based on pharmacogenetic testing are, undoubtedly, not only of scientific interest, but also of practical value. This can be illustrated by phase III of the multicenter clinical trial aimed at studying the efficacy of tiotropium bromide as an alternative to long-acting beta2-agonists for bronchial asthma patients homozygous for ADRB2 gene Arg/Arg16 (Cochran, 1963). This study was based on the concept that the replacement of one of amino acids (Argl6Gly) in the beta2-adrenergic receptor structure results in a more severe course of the disease, a decrease in the therapeutic response and acceleration of receptor desensitization when beta2-agonists are prescribed. That is why the use of M-anticholinergics can help to control the bronchial asthma symptoms for such patients. It has been demonstrated that tiotropium bromide, like salmeterol, significantly improves the lung function as compared to placebo when taken by patients with the genotype homozygous for ADRB2 gene Arg/Arg16 suffering from persistent bronchial asthma that cannot be controlled by inhaled glucocorticoids (Bateman, 2011).

Currently, high attention is paid to the clinical significance of such genetic characteristics of patients as polymorphism of SLC01B1 gene (encoding organic anion transporting polypeptides) in the development of myopathy when using statins, which is necessary to select the dosage regimen based on the pharmacogenetic testing results. Recently, the problem of statin safety — in particular, for the striated muscle tissue — has become increasingly relevant. While rhabdomyolysis, as a dangerous striated muscle complication resulting from the use of statins, is rare (0.15 per 1 million prescriptions), other forms of statin-induced myopathy in patients taking such kind of pharmaceuticals (Sychev, 2016) can occur frequently. In the SERCH study, 85 patients with statin-induced myopathy (90 patients without this complication made up the control group) demonstrated SLC01B 1*5 (c.521T>C) polymorphism as a genetic marker of this complication (Perez-Castrillon, 2010). Patients with the CC genotype taking 80 mg dose of simvastatin developed myopathy 17 times more often than patients with the TT genotype, and patients with the CT

genotype developed myopathy 2.5 times more often than patients with the TT genotype. Currently, the algorithms for personalizing statin use depending on the results of SLC01B1 pharmacogenetic testing (which has become possible for some commercial laboratories in Russia) have been developed.

Pharmacogenetic testing in bioequivalence studies was incorporated in the study of a group of NSAIDs, in particular lornoxicam. According to the results obtained, the presence of CYP2C9*2 and CYP2C9*3 alleles of cytochrome P450 gene in the volunteers' genotype demonstrated variations in the values apparently caused by differences in the volunteers' metabolism associated with the polymorphism of cytochrome P450 gene (CYP2C9). For instance, it was detected that the pharmacokinetics of lornoxicam largely depends on the CYP2C9 polymorphism leading to a significant increase in AUC and the drug half-life, as well as to a decrease in clearance in heterozygotes for cytochrome P450 isoenzyme gene as compared to homozygotes. It has been demonstrated that the occurrence of CYP2C9*2 and CYP2C9*3 alleles among the population of the Russian Federation is 18 %. Since the presence of CYP2C9*2 and CYP2C9*3 alleles (both in heterozygous and homozygous forms) significantly alters the metabolism of lornoxicam, it is considered appropriate to determine the cytochrome P450 gene polymorphism in people in order to reduce the variability of the pharmacokinetic parameters of lornoxicam (Khokhlov et al., 2017).

When conducting pharmacogenetic studies within the framework of CTs, different strategies are possible: the CT design based on genetic testing, the strategy of "enriching" the population of the CT participants, the design involving randomization of all subgroups (Matsui, 2013). The CT design based on genetic testing involves randomization of CT participants into two groups: in the first group, the treatment is adjusted based on genetic testing, while in the second group, the treatment is arranged regardless of the genetic factors. This approach allows assessing the influence of gene polymorphism on the clinical response, and concluding whether the pharmaceutical needs special recommendations taking into account the patient's genotype.

A very good result for a pharmaceutical is when there is no need to take into account the genetic factors during treatment, since the

pharmaceutical can be used irrespective of the patient's genetic status. If genetic factors strongly affect efficacy and safety, it may be necessary to include pharmacogenetic information into the directions for the pharmaceutical use. The strategy of "enriching" the population of the CT participants allows demonstrating the efficacy of a pharmaceutical in a relatively small group of patients by "shutting off" genetic diversity.

This approach can be applied almost throughout the entire CT, from phase I to phase III. First, predominantly homozygous wild-type carriers (the most common genotype) are selected. This is not always possible, but, in any case, the carriers of polymorphisms associated with the altered state of functioning of the protein products of the corresponding genes should be avoided. At later CT phases, the "enriching" strategy can be used to select, conversely, the CT participants with genetically determined deviations in the processes of pharmacokinetics and/or pharmacodynamics of the studied pharmaceutical (such samples allow determining the pharmaceutical dosage for certain individuals depending on their genotype).

The CT design involving the strategy of "enriching" the population of participants, includes the following stages:

1. Initial testing for planned genetic polymorphisms;

2. Only the participants with a certain specific genotype are admitted to take part in the CT;

3. Randomization of the participants admitted to take part in the CT based on the genotypes, and formation of the experimental group and the control group;

4. CTs in the experimental group.

Sometimes the information obtained as a result of pharmacogenetic study is used to "save" the pharmaceuticals that were previously rejected during the CT. For instance, in phase III CT of ximelagatran, an oral anticoagulant and a potent, competitive, reversible direct inhibitor of alpha-thrombin which causes the fibrinogen-fibrin conversion, hepatotoxicity manifestations of an immunological nature were detected. As a result, the pharmaceutical did not pass phase III CT and was not registered.

However, subsequent pharmacogenetic studies demonstrated that the hepatotoxicity of ximelagatran is connected with patients' genetic features, in particular, with the polymorphism of genes of one of the components

of the main histocompatibility complex. Therefore, the pharmaceutical may be used, but not for certain cohorts of patients (or the treatment of such cohorts of patients needs to be adjusted taking into account their individual genetic characteristics).

Thus, as the field of knowledge related to human genetic polymorphism expands, we sometimes get arrays of rather contradictory information, which is currently quite difficult to apply in practice (Khokhlov et al., 2017). There are relatively few algorithms for using pharmacogenetic knowledge in treatment, although their number is constantly increasing (March et al., 2001; Konstantinos, 2020). At the same time, the absence (or presence), in a pharmaceutical, of an obvious variability of the pharmacological response associated with genetic polymorphism is valuable knowledge in itself that must be established by the end of the CT. Pharmacogenetic testing allows, at the initial stages of clinical studies of bioequivalence, excluding from the experimental group the volunteers and/or patients significantly different in pharmacokinetic and pharmacodynamic parameters from the average statistical level of the target group, which, of course, means cost-effectiveness. In the later CT phases, conversely, it is possible to include into experimental groups the patients with genetically induced "deviations" of metabolic parameters, or transport of active components and/or active metabolites of the drug, or changes in the appropriate pharmacodynamic effect. CTs involving pharmacogenetic knowledge can have different designs, and allow expanding the understanding of efficacy and safety of the studied pharmaceutical, and, sometimes, adding the information obtained to the directions for drug use. Pharmacogenetics and CTs of pharmaceuticals can develop in close cooperation, mutually enriching each other (Khokhlov et al., 2017).

III. Biobanking

With the emergence of biobanking, a significant role in the development of state-of-the-art medicine and pharmaceutical industry is increasingly played by the use of collections of biological material for accomplishing research-related and practical tasks.

Comprehensive research directions, including fundamental and clinical research, educational programs, publications, etc., are related to the functioning and development of biobanks (Reznik et al., 2016).

Human biological material stored in biobanks, depending on the goals and needs of the end users, can be biopsy, blood, plasma, urine, fragments of DNA or RNA molecules, bone marrow, etc. The key tasks of biobanks are identification and validation of the diagnostic biomarkers necessary for adequate assessment of a developing pathology and prediction of the prospects thereof in a particular patient or person from the risk group, as well as establishment of links (associations) between the genes and diseases (the degree of associativity), selection of new pharmacotherapeutic targets (PTTs), and creation of innovative (mono- and multitarget) pharmaceuticals (Critchley et al., 2012).

There are several definitions of biobanking. Large international communities, such as the Organization for Economic Co-operation and Development (OECD), the International Society for Biological and Environmental Repositories (ISBER), the European Commission (EC) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) have their own definitions of this concept.

According to the OECD, a biobank is a collection of biological material, and the associated data and information stored in an organized system, for a population or a large subset of a population (The Organisation for Economic Co-operation and Development (OECD), 2006).

In the opinion of the International Society for Biological and Environmental Repositories (ISBER), a biobank is an entity that receives, stores, processes and/or distributes biospecimens, as needed (i.e., it encompasses the physical location of specimens, and the full range of activities associated with its operation) (Campbell, 2012).

The European Commission has its own point of view defining a biobank as an organized collection consisting of biological samples and related data that are of particular importance for fundamental science and the needs of personalized medicine (Zika et al., 2010).

According to one of the leading organizations in the sphere of biobanking at the moment — the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) — biobanks contain biological samples and the associated information that are the essential raw material for

the advancement of biotechnology, human health, and for research and development in life sciences (Assabler and Zatloukal, 2007).

Generalizing the concept of biobanking, one can refer to the widely accepted definition by Kauffmann and Cambon-Thomsen: a biobank is an organized collection of human biological material and associated information stored for one or more research purposes (Kauffmann and Cambon-Thomsen, 2008). At the same time, as genetic technologies develop, the potential goals and objectives of biobanks may expand. Definition of the range of possible, or permissible, objectives lies within the competence of policy makers and legislators. Therefore, approaches to biobanks, biobanking, or biobanking activities may vary (from liberal to conservative ones).

In general, a biobank can be described as a structure consisting of two parts: 1) the biological material that is collected, processed and stored for a long time; 2) the database with demographic and clinical data for each sample, enabling specimen collection, processing, storage, or inventory, and distribution of biological material (Artene et al., 2013).

It should be noted that the BBMRI classification currently distinguishes 2 types of biobanks (Holub et al., 2007; Yuille et al., 2007):

1) population biobanks (prospective biobanks focused on the study of various populations or certain social groups);

2) clinical biobanks (banks of tissue samples and clinical data intended for the study of diseases).

Studying the frequencies of clinically significant genetic polymorphisms in the population is a standard task for population biobanks. Such studies are key for Russia, since its population is characterized by an extremely high heterogeneity of the gene pool (Gorin et al., 2020).

In terms of the source of funding, the following biobank types are distinguished:

A) Public (state-run) biobanks (HUNT, Norway);

B) Private biobanks (deCODE, Iceland);

C) Public-private partnerships (UK Biobank).

At the same time, from the standpoint of sociologists and psychologists, the concept of “biobanking” includes the whole range of social, legal and ethical issues to be resolved as biobanks develop.

IV. Ethical issues of genetic material collection

The ethical and legal conflict associated with the activities of biobanks is due to the fact that the process of receipt, storage and use of biomaterial involves several participants. For example, donors are interested in ensuring privacy and information provision in order to control the use of biobank material (to introduce some ethical and/or other restrictions on access to the samples in connection with the donor's moral or religious views, changes in the donor's social or personal status, or the family's position, etc.)

Biobank owners are interested in autonomous use of material, and in independence from the donors, in order to expand the possibilities for using the results of their activities in science/research and for commercial purposes.

Scientists and researchers are interested in unrestricted and free-of-charge access to biobanks for work in sphere of pharmacogenetics, epidemiology, population studies, etc.

Any biobank is interested in people voluntary transferring their material and signing an informed consent form without strictly determining the purpose of the material use. This is due to the ethical issue arising with regard to biological material use. If a volunteer stipulates the conditions for the use of their genetic material (e.g., defines the scope/range of the experiments in which they are ready to take part), the biobank has to monitor the inclusion of the samples of that particular individual into the pool of the specimen and material for specific studies/trials. It becomes necessary to prevent inclusion of any biological material of that particular individual in some other experiments or further research. This creates organizational, technological and financial difficulties. Moreover, a volunteer, at the stage of publishing the research results (including the results obtained in course of their genetic information processing), may revoke/withdraw their consent for the genetic material transfer and for the use of the information obtained as a result of the genetic material analysis. If this happens, the use of the results becomes ethically illegitimate, and, therefore, the research becomes useless.

The key characteristic feature of international biobanks remains their "disconnection" (lack of integration) due to the absence of uniform legal norms, which significantly complicates the exchange of information between biobanks, and hinders efficient cooperation. Promising international projects are experiencing significant difficulties due to the non-uniformity of legal, ethical and other norms in different countries (Cailfield et al., 2014).

Currently, there exist a number of difficulties with international biobank creation: there are practically no legal norms or laws regulating the work with biological samples. The existing regulations are very different in different countries (Reznik et al., 2016).

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use proposed a harmonized trilateral ICH Guidance entitled *E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* (dated 1 November 2007), and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use developed harmonized ICH *E18 Guideline on Genomic Sampling and Management of Genomic Data* (dated 3 August 2017).

The main purpose of the aforementioned documents is to harmonize the principles of genomic sampling and genomic data management in clinical studies, as well as to increase awareness and provide a reminder regarding the need to respect the rights of participants in connection with the use of their personal information, protection of the data generated, the need to obtain informed consent, and the need to ensure transparency of findings in line with local legislation and regulations. Genomic research can be used at all stages or phases of pharmaceutical development. These documents are in full compliance with ethical requirements.

It is important to be able to integrate [combine] genetic/genomic data with other clinical data for use not only in current clinical studies, but also in the future. Therefore, it is recommended to store samples and data in the appropriate biobanks (Sayamov, 2020).

Key ethics-related concerns traditionally include informed consent, privacy (confidentiality) and data protection issues (Hawkins and O'Doherty, 2013).

According to the World Medical Association, the ethical principles for medical research apply to human subjects, including research on identifiable human material and data; and a physician shall act in the patient's best interest when providing medical care. This implies that collection, storage and use of samples of organs and tissues of a person is impossible without the consent of that person.

In accordance with international agreements and guidelines regarding research ethics (Fortier et al., 2011), informed consent must guarantee voluntary participation and describe the privacy issues. Informed consent consists of three main components: complete/ adequate information, voluntariness [confirmation that the consent is voluntary], and [legal] competence. This means that, before consenting, the biological material donor must clearly and fully understand their role in the study and the study purpose, be aware of the potential risks and side effects, and be able to refuse participation or withdraw from the study at any time. Informed consent is required when the study involves human beings, their genetic material, or personal data. Informed consent must protect the autonomy of an individual. Particular attention should be paid to certain groups of vulnerable people (such as children, elderly people, people with disabilities), and national background/peculiarities should also be taken into account.

There are heated debates around informed consent, and, in particular, its forms (whether it should be universal, or different for each new study taking into account the specifics). The main message is the use of two forms of informed consent in a clinical study. The first one is the "classic" ["traditional"] form providing the patient with the information about the clinical study, and containing all the sections and information required by the existing regulatory documents. The signing of this kind of form confirms the patient's consent and ability to participate in the given clinical study. The second one is the "genetic" form of informed consent. By signing it, the patient allows the use of their biomaterial for genetic research. At the same time, the patient's refusal to sign this kind of form does not limit their ability to participate in the clinical study as such.

Informed consent for the collection and use of genomic samples should permit extended analysis of the samples (e.g., gene set

identification, transcriptome analysis, or complete genome sequencing) regardless of the timing of the analysis.

The ethical principles regarding the information provided to patients are quite extensively described in Article 8 (paragraph *a*) of the *International Declaration on Human Genetic Data*, which says that prior, free, informed and express consent should be obtained for the collection of human genetic data, human proteomic data or biological samples, whether through invasive or non-invasive procedures, and for their subsequent processing, use and storage, whether carried out by public or private institutions. Informed consent is an extremely important document in clinical studies/trials not only because it can be withdrawn/revoked at any time, but also from the standpoint of privacy/confidentiality, or the possibility of using data for other research purposes for many years, etc.

The analysis of the clinical trial practice in Russia has demonstrated that almost all informed consent forms lack a section concerning the human right to decide whether or not to be informed about the results and consequences of the genetic analysis, as stipulated in the aforementioned document (Article 5, section *c*). However, this can be extremely important for the subsequent medical observation of the patient, for the selection of an appropriate occupation by the person (patient), for the patient's awareness of the undesirable/adverse effects of drug therapy associated with the peculiarities of genetically controlled metabolism, etc. (Sayamov, 2020).

Another important ethical issue of biobanking is confidentiality. Any biobank works with anonymized information about citizens. The problem of biobanking is how to reconcile the autonomous right of each person to manage their genetic material (including the right to determine what types of research are acceptable for that particular person) with the tasks of generating mass knowledge. This problem cannot be resolved using a standard algorithm for any biobank. Therefore, each biobank, depending on its purpose, the way of funding, and the scale of collections, always has to address the issues related to ethical and legal regulation.

On the other hand, there are proposals to create informed consent forms without any guarantees of anonymity, privacy and confidentiality

(Varkhotov et al., 2016). In the near future, the existing problems may be resolved through development of unified rules (protocols) and standards for working with biological specimen, i.e., the introduction of harmonization mechanisms allowing free exchange of biological specimen, and the information related thereto, following universal algorithms at the global level (Lunshof et al., 2008). The importance of harmonization is determined by the need to eliminate double interpretation of the same results by researchers in different countries through introducing strict standards for all biobanks (Reznik et al., 2016).

In recent years, hundreds of publications dealing with the link (association) between certain polymorphisms and the efficacy of pharmaceuticals for certain pathologies have appeared. Knowledge is being accumulated accompanied by creation of many databases and data banks including the results generated in course of clinical trials and treatment of diseases. Unfortunately, the protocols of IMCT (International Multicenter Clinical Trials), which are also performed in Russia, do not include any "feedback", and even the chief researchers of the studied pharmaceutical learn the genomic test results, including the possible associations with certain pathologies, after a long time and only from publications. Naturally, patients do not have this information either, which calls into question the ethics of such processes (Sayamov, 2020). This is important, since some genetic polymorphisms mean the need for changing the doses of the studied pharmaceuticals, or are significant for preventing undesirable side effects. Therefore, this information should be known not only to the doctor, but to the patient as well. However, there is almost never any feedback on the results of clinical studies involving pharmacogenetic testing with personal follow-up information provision to the patient.

Therefore, the current trends of genetic research expansion in the study of pharmaceuticals require further improvement of the regulatory framework.

V. Differences in the global and Russian practice of genetic material circulation

Currently, Russia is paying increasing attention to the development of science-intensive biomedical, genetic, and cellular technologies, which are impossible without developing biobanks. However, in terms of regulation, the issue of genetic material circulation in the Russian Federation is a complex problem obviously lacking appropriate legislative framework (Kosilkin, 2020).

While in Russia the authorities in charge of ethics reviews remain wary about permission to collect genetic material from clinical trial participants, in global practice the situation is the opposite. For example, Regulation (EU) (European Commission, 2017) encourages collection of biological samples for future research. In particular, *ICH E18 Guideline on genomic sampling and management of genomic data* (International Council for Harmonization, 2017) points out that the general approach of regulators in ICH regions is to encourage genomic research "which may or may not be pre-specified in the clinical study objectives at the time of collection" (E18 Section 1.2). In addition, it explicitly states that "genomic research could be used in all phases of drug development to assess genomic correlates of drug response, and to understand mechanisms of disease or drug pharmacology".

It also says that "Genomic research can be conducted during or after a clinical study. It may or may not be pre-specified in the clinical protocol" (E18 Section 1.3). The Guideline allows all kinds of work with the collected biomaterial within the scope of an informed consent (E18 Section 1.3), however, it recommends using a broad form of informed consent "permitting sharing and distribution" (E18 Section 4.2), and also permitting broad analysis of the samples "regardless of the timing of analysis. Ideally, informed consent should allow for broad use of the samples, such as assay development, disease research, drug response, or pharmacovigilance" (E18 Section 5).

At the same time, according to the Guideline, in some cases it is allowable not to communicate the results of future studies to the patients who provided the biomaterial (E18 Section 6), since the focus of the recommendation to collect biomaterial for future studies is not the

benefit of a particular patient, but a purely scientific goal of maximizing the value of the collected samples and the data generated from them (E18 Section 1.4). ICH E18 Guideline recommends collecting biomaterial at all phases and for all studies, if possible, from all participants (E18 Section 1.4): "With advances in science and increased awareness of the impact of genomics, there is a need and an opportunity to maximize the value of the collected samples and the data generated from them. Therefore, genomic sample acquisition is strongly encouraged in all phases and studies of clinical development. Moreover, the quality of genomic research is dependent upon unbiased systematic collection and analysis of samples, ideally from all subjects participating in the trial, in order to fully represent the study population" (International Council for Harmonization, 2017).

When a clinical trial participant gets the right to choose whether to permit the collection of their genetic material specified in the Patient Information Sheet within an informed consent form, they become able to independently make a decision about their readiness to make a specific contribution to science in the form of their biomaterial, which, as it accumulates in biobanks, will form the basis for the development of new pharmaceuticals and saving the lives of future generations.

At the same time, apart from the individual interests of researchers, as well as the interests of participants in clinical trials/studies, there exist some public and state (government) interests that do not always coincide. In addition to containing the information about a person and their genotype, the human genome allows obtaining (especially if a sufficiently large number of biosamples or relevant information about them is available) the data characterizing certain specific features, peculiarities, on the basis of which it is hypothetically possible to accomplish tasks aimed at solving both clinical and other problems.

For instance, in Israel, genetic data are successfully used to deal with the issue of belonging to a particular group, ethnicity. In Iceland, genetic information is used in order to avoid inbreeding.

The use of genetic technologies for purposes other than medical, and insufficient control over circulation of genetic information are beginning to pose a threat to citizens in labor relations and when dealing with certain types of insurance (first of all, voluntary health

insurance). The possibilities of discrimination against certain groups of people based on the probability theory, as well as the use thereof in actuarial calculations, are emerging.

The stored genetic information is also of interest to law enforcement authorities and courts, as it allows them to enhance the efficiency of handling their tasks.

A standalone problem is the emergence of biohacking and biocrime involving use of personal genetic information for criminal purposes (blackmail, bribery, disclosure of confidential information, etc.).

Besides, genetic information can be used in continuous attempts to develop biological and other selective-action weapons, as well as to determine the strategy and tactics of modern (including "hybrid") warfare.

The foregoing necessitates definition of a corridor of possibilities in this sphere, as well as differentiation of legal frameworks for circulation of certain types (units) of genetic information. This also brings about the issue of restrictions and prohibitions both in the sphere of genetic information circulation for accomplishing research-related and other tasks, as well as in related areas. For example, the choice of a biobanking model (liberal or conservative) is conditioned, on the one hand, by the originally formulated requirements for biological objects, biosamples of human origin, and, on the other hand, by understanding the technological possibilities of digitizing such objects (physical technical control is more difficult to ensure in this instance than for physical objects stored in biobanks).

In this connection, in addition to dispositive [discretionary] norms and contractual relations in this sphere, a set of imperative [peremptory] norms and requirements aimed at ensuring public interests in this area, will be formed.

Whereas the United States and some countries of Western Europe have "liberal" legislation in this sphere, the Asian countries — primarily China — stick to a "conservative" approach (which applies both to the sphere of biobanking and circulation of genetic information, and information in general).

It should also be noted that the major flow of biomaterials and information about biological objects goes into the US and some other

countries, but not out of them. In order to protect the US interests (including the sphere of information), special tools aimed at restricting the outflow of controlled materials, technologies, and information, can be actively applied. The US have a fairly developed legislation in the sphere of control over foreign economic activity in general, as well as technology transfer. At some points in time, Russia borrowed some of the legal means and mechanisms to protect its interests as well.

Some of the examples of such regulations are: Federal Law No 183-FZ [in Russian: 183-ФЗ] *On Export Control* dated 18 July 1999; Federal Law No 164-FZ [164-ФЗ] *On the Foundations of State Regulation of Foreign Trade Activities* dated 8 December 2003; Federal Law No 281-FZ [281-ФЗ] *On Special Economic Measures and Coercive Measures* dated 30 December 2006.

They do not directly mention the possibility of introducing (permanent or temporary) prohibitions or restrictions in relation to the issues under consideration, however, Russia can use some general or special legislative provisions with regard to foreign economic activities, if necessary.

For instance, a special economic measure under the Federal Law No 281-FZ *On Special Economic Measures and Coercive Measures* dated 30 December 2006 is the prohibition or refusal to participate in international research or research-and-engineering programs and projects of a foreign country.

Opportunities that have emerged in connection with the development of synthetic biology are becoming a standalone problem for legislators requiring a detailed study in order to develop sound recommendations. Whereas before its advent the efforts of researchers were focused on isolating, studying, digitizing a biological object, as well as storing the object itself and (or) the information about it, the development of synthetic biology has brought about a hypothetical opportunity — drawing on information and existing technologies (genome editing, bioprinting, cloning, etc.) — to reproduce a biological object only on the basis of information about it or create a new biological object, a living system. Therefore, the availability of information and technologies changes the paradigm of many processes, both opening up

new opportunities and bringing about new risks and threats for people, society, and the state.

Based on the above, the definition of the basic model of circulation of biomaterial, genetic material, as well as biological and genetic information, needs to take into account the entire range of private, public, and state interests.

VI. Conclusion

The aspects of genetic material use in clinical studies/trials analyzed here allow highlighting the complex and controversial problems faced by both pharmaceutical manufacturers and regulatory authorities. The existing differences in the legislative regulation of genetic material circulation in different countries emphasize the high relevance of the issue and allow finding the ways to harmonize international and national law in the sphere of genetic information circulation in general, and in the sphere of biobanking, taking into account both private and public interests, traditions, and development priorities, as well as risks and threats in this area.

References

1. Andersen, V. et al., (2009). Polymorphisms in the xenobiotic transporter Multipharmaceutical Resistance 1 (MDR1) and interaction with meat intake in relation to risk of colorectal cancer in a Danish prospective case-cohort study. *BMC Cancer,* 9, p. 407.

2. Artene, S.A., Ciurea, M.E., Purcaru, S.O. et al., (2013). Biobanking in a constantly developing medical world. *The Scientific World Journal*, 343275, 1–4.

3. Assabler, M., Zatloukal, K., (2007). Biobanks: transnational, European and global network. *Brief. Funct. Genomic. Proteomic,* 6(3), pp. 193–201.

4. Avdeyev, R.M. et al., (2010). Genetic Polymorphism and Ethnic Aspects of Pharmacogenetics. *Medical Genetics*. 5(6), pp. 11–15. (In Russ.).

5. Bateman, E.D., Kommann, O., Schmidt P. et al., (2011). Tiotropimn is noninferior to salmeterol in maintaining improved lung function in

B16-Arg/Arg patients with astluna. *Journal of Allergy and Clinical Immunology*, 128(2), pp. 315–322.

6. Borodulin, V.D. et al., (2011). Association of Polymorphism of CYP2D6 and CYP2C9 Genes Encoding the Proteins of Cytochrome P-450 with the Degree of Arterial Hypertension. *Saratov Journal of Medical Science and Research*, 8(4), pp. 933–937. (In Russ.).

7. Cambon-Thomsen, A., Rial-Sebbag, E. and Knoppers, B.M., (2007). Trends in ethical and legal frameworks for the use of human biobanks. *The European Respiratory Journal*, 30(2), pp. 373–382.

8. Campbell, L.D. (ed.), (2012). *2012 Best Practices for Repositories Collection, Storage, Retrieval, and Distribution of Biological Materials for Research*. 3rd edn. International Society for Biological and Environmental Repositories. *Biopreservation and Biobanking*, 10(2), pp. 79–161, doi: 10.1089/bio.2012.1022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24844904.

9. Caulfield, T., Burningham, S. and Joly, Y. et al., (2014). A Review of the Key Issues Associated with the Commercialization of Biobanks. *Journal of Law and Biosciences*, 1(1), pp. 94–110.

10. Chinn, L. and Kroetz, D., (2007). ABCB1 Pharmacogenetics: Progress, Pitfalls, and Promise. *Clinical Pharmacology & Therapeutics*, 81(2), pp. 265–269.

11. Cochran, W.G., (1963). *Sampling Techniques*. 2nd ed. New York: John Wiley and Sons, Inc.

12. Collet, J.P., Hulot, J.S., Pena, A. et al., (2009). Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: A cohort study. *Lancet*, 373, pp. 309–317.

13. Critchley, C., Nicol, D., Otlowski, M. and Stranger, M., (2010). Predicting intention to biobank: a national survey. *The European Journal of Public Health*, 22(1), pp. 139–144.

14. Ernest, S. and Bello-Reuss, E., (1998). P-glycoprotein functions and substrates: possible roles of MDR1 gene in the kidney. *Kidney International Supplements*, 65, pp. 11–17. (In Russ.).

15. European Council. *Ethical considerations for clinical trials on medicinal products conducted with minors*. (2017). Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human

use. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf (Accessed 21 April 2021).

16. European Council. *Ethics for researchers. Facilitating research excellence in FP7.* (2013). Luxembourg: Publications Office of the European Union. Available at: https://ec.europa.eu/research/participants/data/ref/fp7/89888/ethics-for-researchers_en.pdf (Accessed 21 April 2021).

17. Fortier, I., Doiron, D., Burton, P. et al., (2011). Invited commentary: consolidating data harmonization — how to obtain quality and applicability. *American Journal of Epidemiology,* 174, pp. 261–264.

18. Gorin, I.O., Petrushenko, V.S., Zapisetskaya, Yu.S., Koshel', S.M. and Balanovskiy, O.P., (2020). Population Biobank Application for Analyzing the Frequencies of Clinically Significant DNA Markers in the Population of Russia: Bio-informational Aspects. *Cardiovascular Therapy and Prevention*, 19(6), pp. 27–32, doi:10.15829/1728-8800-2020-2732.

19. Hawkins, A.K. and O'Doherty, K.C., (2011). «Who owns your poop?» Insights regarding the intersection of human microbiome research and the ELSI aspects of biobanking and related studies. *BMC Medical Genomics*, 11(4), p. 72.

20. Holub, P., Swertz, M., Reihs, R., van Enckevort, D., Müller, H. and Litton J.E., (2016). BBMRI-ERIC Directory: 515 Biobanks with Over 60 Million Biological Samples. *Biopreserv Biobank,* 14(6), pp. 559–562.

21. Karpenko, M.A., (2007). *Arterial Hypertension: Age, Gender and Genetic Peculiarities. Doctoral Dissertation (Doctor of Medical Science).* Moscow. (In Russ.).

22. Kauffmann, F. and Cambon-Thomsen, A., (2008). Tracing biological collections: between books and clinical trials. *JAMA*, 299(19), pp. 2316–2318.

23. Khokhlov, A.L. et al., (2012). Importance of Determining the Polymorphisms of the Genes Responsible for the Activity of Angiotensin-Converting Enzyme in the Patients with Arterial Hypertension and Chronic Cardiac Insufficiency for Optimizing the Arterial Hypertension Treatment Standards. *Problems of Standardization in Healthcare,* 4, pp. 41–44. (In Russ.).

24. Khokhlov, A.L. et al., (2017). *Theoretical and Practical Foundations for Conducting Research of Generic Drugs: Monograph*. Moscow-Yaroslavl-Prague: Photolife Press. (In Russ.).

25. Khokhlov, A.L., Kukes, V.G. and Sychev, D.A., (2016). *Approaches to Pharmacogenetic Studies of the Diseases Associated with Lipid Metabolism Disorders and Atherosclerosis*. Moscow: Yaroslavl Press. (In Russ.).

26. Khokhlov, A.L., Pozdnyakov, N.O. and Rybachkova, Yu.V., (2016). *Importance of Pharmacogenetic Studies for Various Forms of Cardiac Ischemia*. Yaroslavl: Remder Press. (In Russ.).

27. Klaassen, C.D. et al., (2010). Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacological Reviews*, 62(l), pp. 1–96.

28. Konstantinos, G., (2020). Regulatory Aspects of Genomic Medicine and Pharmacogenomics, in Patrinos, G.P., (ed.) *Applied Genomics and Public Health*. Elsevier: Academic Press, pp. 345–360, doi:10.1016/b978-0-12-813695-9.00020-0.

29. Kosilkin, S.V., (2020). Experience of Legal Regulation of Biobank Activities in Global Practice and Development of Russian Legislation. *Courier of Kutafin Moscow State Law University (MSAL),* 4(68), pp. 79–87. (In Russ.).

30. Kukes, V.G., Bochkov, N.P., (2007). *Clinical Pharmacogenetics*. Moscow: Geotar-Media Press. (In Russ.).

31. Lunshof, J.E., Chadwick, R., Vorhaus, D.B. et al., (2008). From genetic privacy to open consent. *Nature Reviews Genetics*, 9(5), pp. 406–411.

32. March, R., Cheeseman, K., and Doherty, M., (2001). Pharmacogenetics — legal, ethical and regulatory considerations. *Pharmacogenomics,* 2(4), pp. 317–327, doi:10.1517/14622416.2.4.317.

33. Matsui, S., (2013). Genomic Biomarkers for Personalized Medicine: Development and Validation in Clinical Studies. *Computational and Mathematical Methods in Medicine*. Available at: https://pubmed.ncbi.nlm.nih.gov/23690882/.

34. Morozova, T.E. et al., (2016). Pharmacogenetic Approaches to Forecasting the Efficacy and Safety of Arterial Hypertension Pharmacotherapy. *Healthcare Practitioner*, 3, pp. 77–81. (In Russ.).

35. Ozawa, S., Soyama, A., Saeki, M., Fukushima-Uesaka, H., Itoda, M., Koyano, S., Sai, K., Ohno, Y., Saito, Y. and Sawada, J., (2004). Ethnic Differences in Genetic Polymorphisms of CYP2D6, CYP2C19, CYP3As and MDR1/ABCB1. *Drug Metabolism and Pharmacokinetics*, 19(2), pp. 83–95.

36. Perez-Castrillon, J.L., AbadManteca L., Vega G. et al., (2010). Vitamin D levels and lipid response to atorvastatin. *International Journal of Endocrinology*. Available at: https://pubmed.ncbi.nlm.nih.gov/20016682/ [Accessed 21 April 2021].

37. Ramenskaya, G.V., Faynshteyn, S.L. and Sychev, D.A., (2007). Importance of Change in the Functional Activity and the Amount of Expressed P-glycoprotein in Drug Pharmacokinetics. *Experimental and Clinical Pharmacology*, 70(1), pp. 72–80. (In Russ.).

38. Reznik, O.N., Kuz'min, D.O., Skvortsov, A.E. and Reznik A.O., (2016). Biobanks: an Invaluable Resource for Transplantation. History, Current State, Prospects. *Bulletin of Transplantology and Artificial Organs*, (4)XVIII, pp. 123–132. (In Russ.).

39. Sayamov, Yu.N., (2020). *Bioethics and the Global Challenges. Documents and Reflections*. Moscow: Veche publ. (In Russ.).

40. Scientific Centre for Expert Evaluation of Medicinal Products Federal Institution. *Methodology Guidelines of the Scientific Centre for Expert Evaluation of Medicinal Products Federal Institution*? (2012). Available at: http://rdg-cro.com/wp-content/uploads/2012/07/Guidelines-for-conducting-bioequivalence-studies-in-Russia.pdf [Accessed 21 April 2021].

41. Scientific Centre for Expert Evaluation of Medicinal Products Federal Institution. *Evaluation of Bioequivalence of Drugs*. (2008). Methodology Guidelines of the Scientific Centre for Expert Evaluation of Medicinal Products Federal Institution. Available at: http://rdg-cro.com/wp-content/uploads/2012/07/Guidelines-for-conducting-bioequivalence-studies-in-Russia.pdf [Accessed 21 April 2021].

42. Sokolov, A.V., Kukes, V.G., Bunyatyan, N.D. et al., (2015). Pharmacokinetic Approach to the Issue of Drug Interchangeability. *Biomedicine,* 3, pp. 43–51.

43. Sychev, D.A. (ed.), (2009). *Recommendations for Pharmaceutical Companies on the Study of Biotransformation and Transporters of New*

Pharmaceuticals: Research Design, Data Analysis and Information Entry into Directions for Use. Available at: http://www.regmed.ru/ Content/ Doc.aspx?id=26a9128c-ee32-4469-9c64-5c666339049e [Accessed 21 April 2021].

44. Sychev, D.A. et al., (2011). Pharmacogenetic Technologies of Personalized Medicine: Optimization of Drug Administration. *Terra Medica,* 1, pp. 4–9.

45. Sychev, D.A., (2016). Pharmacogenetic Testing in Clinical Trials. *Pharmacogenetics and Pharmacogenomics*, 1, p. 13. (In Russ.).

46. The International Council for Harmonisation. *ICH Harmonized Guidelines. ICH E18 Guideline on Genomic Sampling and Management of Genomic Data*. (2017). Available at: https://www.ema.europa.eu/en/ich-e18-guideline-genomic-sampling-management-genomic-data. [Accessed 21 April 2021].

47. The Organisation for Economic Co-operation and Development (OECD). *Creation and Governance of Human Genetic Research Databases. Glossary of Statistical Terms*. (2006). Available at: http://stats.oecd.org/glossary/detail.asp?ID=7220 [Accessed 1 Aug 2016].

48. Varkhotov, T.A., Gavrilenko, S.M., Stambol'skiy, D.V., Ogorodova, L.M., Bryzgalina, Ye.V. and Alasaniya, K.Yu., (2016). Objectives of Social and Humanitarian Support during Creation of a National Depository Bank for Biomaterials in Russia. *Issues of Philosophy*, 3, pp. 124–138. (In Russ.).

49. Yakusheva, E.N., Chernykh, I.V. and Biryukova, A.S., (2011). Characteristics of P-glycoprotein as a Medication Transporter. *Pavlov Russian Medicine and Biology Bulletin*, 3, pp. 142–148. (In Russ.).

50. Yuille, M., van Ommen, G.-J., Bréchot, C. et al., (2007). Biobanking for Europe. *Brief Bioinform*. 9 (1), pp. 14–24, doi: 10.1093/bib/bbm050.

51. Zika, E., Paci, D., Bäumen, S. et al., (2010). *Biobanks in Europe: prospects for harmonisation and networking. JRC Scientific and Technical Reports*. L.: Publications Office of the European Union. Available at: http://www.eurosfaire.prd.fr/7pc/doc/1280153287_biobanks_eu_jrc57831.pdf [Accessed 1 Aug 2016].

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