INFORMATIZATION AND MATHEMATICAL MODELING OF BIOPHARMACEUTICAL RESEARCH

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Introduction. The development of the mathematical theory of optimal management, computational optimization methods, and the rapid development of computer technologies have created a theoretical and instrumental basis for building mathematical models of biopharmaceutical research.

Carrying out quantitative measurements and, especially, interpreting the results of pharmaceutical research makes it possible to significantly increase the efficiency of processing the results, precisely the use of mathematical modeling methods with the help of computer technologies.

Purpose: to reveal the importance of informatization and features of application and mathematical modeling in biopharmaceutical research

Research methods: methods of mathematical modeling, models and methods of biopharmaceutical research.

Research results and their discussion. Today, modeling of scientific research is the means that allows establishing deep and complex relationships between theory and experiment. Over the last hundred years, experimental methods of scientific research began to encounter a number of limitations, and it turned out that conducting some research in principle is impossible without modeling. This is caused by the following factors:

– intervention in biological systems in in vivo studies may lead to the impossibility of establishing the causes of the changes that occur;

– some theoretically based experiments cannot be carried out due to the insufficient level of development of experimental equipment;

– a number of experiments at the stage of clinical research, which must be conducted on humans, should be rejected on moral, ethical and legal issues.

One of the modeling methods that makes it possible to minimize the above problems is mathematical modeling. Mathematical models are a set of formulas and equations that describe the properties of the object under study. As a rule, models use systems of differential equations that describe dynamic processes characteristic of living nature, as well as systems of linear and nonlinear algebraic equations or inequalities.

Mathematical modeling (English – mathematical modeling, Deutsch – mathematische Modellierung) is a method of studying processes or phenomena by creating their mathematical models and studying these models. The basis of the method is the identity of the form of the equations and the unequivocal relationship between the variables in the equations of the original and the model, i.e., their analogy. Mathematical models are studied with the help of computers.

Mathematical modeling is the process of building and studying mathematical models. Since the mathematical model is a virtual mathematical construction, created on the basis of experimental data, it is given all the properties of a real object. Mathematical models from the middle of the 20th century. are effectively used in a number of technological areas and have already managed to prove that with the help of mathematical modeling it is possible to find optimal engineering solutions with high accuracy, predict the possible results of certain processes, and make the most justified decisions.

The first mathematical models in the field of scientific research of pharmacology and analysis of clinical data began to be developed and applied in practice at the beginning of the 70 years of the 20th century. The new scientific discipline was called "pharmacometrics" and quickly took an important place among the recognized and popular methods of drug development.

The main feature of this discipline can be considered a kind of synthesis of pharmacology and advanced statistical methods, which allows to conduct quantitative analysis of data on the effect of drugs and the development of diseases both at the individual and population level, and to use the maximum amount of information to understand the processes occurring in the interval between taking the drug and the body's response.

Applying pharmacometric methods of drug development, it is possible to answer a number of questions, for example: what doses are optimal for basic clinical studies; to which groups of patients should the drug be targeted; whether dosage changes are required for certain subgroups. Pharmacometric plays a major role in the calculation (taking into account numerous pharmacokinetic/pharmacodynamic studies) of dosage. It is thanks to it that the recommendations for taking drugs, reflected in the instructions and on the packaging of medicines, are created.

Pharmacometric methods are also used during the registration of new drugs. Regulatory bodies of the USA and Europe actively use pharmacometric methods to make decisions related to the labeling and certification of drugs: for the first time, a guide to the use of this scientific method in the process of drug development was created in the FDA's clinical pharmacology department. Thus, the use of this method in the XXI century. entered the world standards of the pharmaceutical industry.

With the development of computer technologies, mathematical models became more and more complex. And this made it possible to significantly expand the scope of their application. Mathematical modeling is used today at various stages of the creation of innovative medicines, and at each stage different types of mathematical models are used. Thus, biological models in the early stages of targeted therapy make it possible to quantitatively assess the interaction of the drug with the target and the speed of its distribution in the body. Pharmacological models make it possible to choose the optimal dose for different patient populations, to determine the therapeutic window with maximum accuracy.

At the final stages of clinical research, where research is conducted on large groups of patients with a wide spread of individual characteristics, statistical models are used. This allows obtaining a quantitative prediction of effects and optimizing the design of clinical trials.

Epidemiological modeling studies groups of patients taking into account specific characteristics - depending on demographic characteristics, living conditions and other factors. And with the help of economics, models of market behavior and decision-making mechanisms are developed, which allow finding the optimal price and strategy for bringing the drug to the market.

All processes in the human body are subject to the basic laws of biology, biophysics and chemistry. And this means that its main characteristics and regularities can be described by mathematical formulas and equations and create a computer model of individual cellular mechanisms, receptors, tissues, a single organ, system and the whole organism as a whole, if the drug is of general action. Various companies also simulate virtual patients to monitor the state of the disease, evaluate the effect of various drugs on its course and on the vital systems of the body.

New methods and algorithms that make it possible to obtain consistent multifactorial experimental plans, to form a stable structure of the regression equation, a priori unknown to the researcher, and to estimate the coefficients of the statistical model in the conditions of the initial multicollinearity of the factors make it possible to solve problems in a real system setting. Such calculations are quite complicated if the informatization of pharmaceutical research processes is not ensured. Implementation of pharmaceutical research monitoring systems provides an opportunity to simultaneously correct invalid experimental data and highlight possible errors in measurement or interpretation of indicators.

Let's consider two key approaches to mathematical modeling of scientific research in biopharmaceutics and pharmacology:

– population models that have proven themselves well in pharmaceutical development, especially for the interpretation of pharmacokinetics and pharmacodynamics data;

– systems pharmacology models that allow integrating data on pathophysiology, regulation of signaling pathways, and distribution of drugs in the body (today known as physiologically based pharmacokinetic models).

In order to combine the characteristics of these two approaches, it is necessary to create integrated modeling platforms. These should be platforms for mathematical modeling of scientific drug research, which will be used as key tools to support decision-making in the development of new drugs.

The application of such platforms in scientific research to solve numerous questions regarding the selection of molecules, dosing and dose planning, selection of the therapeutic window, selection of biomarkers, selection of patient populations, studies of combination therapy, optimization of study design.

Thus, with the help of a special platform of mathematical modeling in the process of developing new drugs, it will be possible to make more informed decisions when selecting options, to choose the most promising molecules to be studied, to find the most suitable targets for drugs, to evaluate the effect of substances on the body.

The cost of such platforms is two orders of magnitude higher than the cost of software products that we are used to, but the reduction in time and labor costs more than compensates for it if research and development activities are carried out on an ongoing basis. Of course, completely abandoning instrumental research, from in vivo experiments, even in the more distant perspective, is unlikely to succeed, since practice remains the criterion of truth for natural-scientific research.

Today, out of 10,000 promising molecules, only one becomes a medicine. Experts note a negative trend towards an increase in the number of failures during the second and third phases of clinical trials. The probability of approval of a new drug after the first stage is 6%, so only 1 in 17 drugs successfully passes all phases of clinical trials. This deals a serious blow to the research and development activities of pharmaceutical companies, because the cost of such studies can reach several tens of millions of dollars. For this reason, many companies are forced to freeze or completely stop their innovative developments.

In some cases, a computer experiment based on real data allows predicting the side effects of a substance that will be revealed only in the future, although it does not cancel the stage of preclinical research of medicinal products on experimental animals and conducting a cycle of clinical research during its registration.

The bar for drug safety is high, and hence there is considerable risk and uncertainty: no pharmaceutical company that conducts development has any guarantees of success and does not know for sure whether the research costs will be justified.

When creating new drugs, mathematical modeling and informatization of scientific research also have a number of advantages compared to traditional research methods. They make it possible to theoretically assess and quantify the impact of a substance on the entire organism as a whole, even on those organs and systems that it does not directly affect, but which may be affected indirectly through complex and long-term interactions inherent in biological systems.

The use of mathematical modeling today is one of the most promising ways to increase the efficiency of the development of new drugs. Mathematical modeling methods make it possible to reduce risks at all stages of drug creation and show the most likely ways of prospects for continuing research

The use of mathematical models in the development of innovative drugs allows you to save resources and avoid many risks. By itself, modeling does not cancel clinical trials, but allows to optimally develop their design and correctly interpret the results. Thanks to this, it is often possible to reduce the number of test failures. The application of modeling is especially important during the transition from the research part of drug development to the proof-of-concept. As you know, the first phases of clinical trials take place on limited samples of healthy volunteers (phase I) or patients (phase II).

Thus, to reduce the risk of failure of expensive phase III trials, it is critical to use all the information accumulated earlier in scientific research, as well as in phases I and II. Mathematical models allow such integration. As a result, it helps researchers to approach the key issues of new drug development – the choice of dose and route of administration – in the most prepared way and make the most informed decisions.

Scientists (*Ponomarenko L.M., Davtyan L.L., Babintseva L.Yu., Ukraine, 2009*) prove that ensuring the minimization of the number of experiments in biopharmaceutics is possible only with high reliability and reliability of research results. Therefore, an urgent task is the development of data analysis methods in the field of statistics, mathematical modeling of multifactorial pharmacological research, multi-criteria optimization, plans of experiments, stable evaluation of the structure and coefficients of models.

Conclusions. The use of mathematical modeling in biopharmaceutical research is associated with the need to make quick, objective and balanced decisions regarding the further development of drugs. These decisions have specific scientific, experimental and economic consequences. It is important to determine the limit of possibilities of modeling methods and its effectiveness in combination with the experimental component.