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ФАРМАЦЕВТИКА САЛАСЫНДАҒЫ МАТЕМАТИКАЛЫҚ ЖӘНЕ КОМПЬЮТЕРЛІК МОДЕЛЬДЕУ

MATHEMATICAL AND COMPUTER MODELING IN THE PHARMACEUTICAL INDUSTRY

МАТЕМАТИЧЕСКОЕ И КОМПЬЮТЕРНОЕ МОДЕЛИРОВАНИЕ В ФАРМАЦЕВТИЧЕСКОЙ ОТРАСЛИ

Abstract*. Mathematical and computer modeling is one of the most powerful tools for analyzing and designing various technological processes, including the pharmacological process, which allows you to save resources and prevent many risks in the production of innovative medicines. The use of such models is especially necessary during the transition from the research to the production stage of the release of medicines. This article discusses the technological process of drug production using the example of the drug "Atenolol". On the basis of certain parameters of this drug, a mathematical model is built, where a complex indicator of the assessment of the quality of the technological process is calculated. When calculating the complex quality indicator, the following main parameters are used: drying temperature, drying time, drug formation coefficient, humidity, strength, decomposition, grinding, integrity. The mathematical and computer models created as a result of the research will improve the efficiency of quality management of the technological process of manufacturing medicines.*

Keywords: *mathematical model, drug preparation technology, computer model, drug quality, technological process.*

Аңдатпа*. Математикалық және компьютерлік үлгілеу әртүрлі технологиялық үдерістерді талдау және жобалау үшін қолданылатын ең қуатты құралдардың бірі болып табылады. Соның ішінде фармакалогиялық үдеріс кезінде шикізаттарды үнемдеуге және жаңа дәрілік препараттарды өндіруде көптеген қауіптердің алдын алуға мүмкіндік береді. Мұндай модельдерді қолдану әсіресе зерттеу кезеңінен дәрілік заттарды шығарудың өндірістік кезеңіне өту барысында қажет. Бұл мақалада «Атенолол» препаратының мысалында препаратты өндірудің технологиялық үдерісі қарастырылады. Осы препараттың белгілі бір параметрлері негізінде математикалық үлгі құрылған, онда технологиялық үдерістің сапасын бағалаудың кешенді көрсеткіші есептелген. Сапаның кешенді индикаторын есептеу кезінде келесі негізгі параметрлер қолданылды: кептіру температурасы, кептіру уақыты, препараттың пайда болу коэффициенті, ылғалдылық, беріктік, ыдырау, ұнтақтау, тұтастық. Зерттеу нәтижесінде құрылған математикалық және компьютерлік үлгілер дәрілік заттарды дайындаудың технологиялық үдерісінің сапасын басқарудың тиімділігін арттыруға мүмкіндік береді.*

Түйін сөздер: *математикалық үлгі, дәріні дайындау технологиясы, компьютерлік үлгі, дәрі препаратының сапасы, технологиялық үдеріс*

Аннотация*. Математическое и компьютерное моделирование является одним из самых мощных инструментов анализа и проектирования различных технологических процессов, в том числе и фармакологиче-*

ского процесса, которое позволяет сэкономить ресурсы и предотвратить многие риски при производстве инновационных лекарственных препаратов. Использование таких моделей особенно необходимо при переходе от исследовательского к производственному этапу выпуска лекарственных средств. В данной статье рассматривается технологический процесс производства препарата на примере лекарства «Атенолол». На основе определенных параметров данного препарата строится математическая модель, где ведется расчет комплексного показателя оценки качества технологического процесса. При расчете комплексного показателя качества используются следующие основные параметры: температура сушки, время сушки, коэффициент образования лекарственного средства, влажность, прочность, разложение, измельчение, целостность. Созданные в результате исследования математические и компьютерные модели позволят повысить эффективность управления качеством технологического процесса изготовления лекарственных средств.

Ключевые слова: *математическая модель, технология приготовления лекарственного средства, компьютерная модель, качество лекарственного средства, технологический процесс.*

Introduction. The main purpose of pharmaceutical production is to provide consumers with high-quality medicines. Even though their quality is controlled by both manufacturers and state certification bodies, it is quite possible that products that do not meet the quality requirements of medicines will be supplied to the consumer market. Such medicines can not only help a person, but also harm his health.

Creating medicines is an expensive and risky process. Consulting companies estimate that it is necessary to spend large sums to develop a successful drug, and it takes decades to manufacture. Despite such costs, many of these drugs still cannot pass clinical trials. The number of refusals during registration of medicines is increasing. This means that in the future, due to the high risk, it is possible to reduce the financing of this health industry.

Mathematical modeling is currently one of the most relevant areas in scientific research. High demands are placed on modern medicine, as well as on the qualifications of doctors and the methods used [1-3]. The choice of some mathematical models in the description and study of mathematical objects depends on the individual knowledge of the specialist and the specifics of the problem being solved.

The use of mathematical models in the production of innovative drugs saves resources and prevents numerous risks [4,5]. Modeling alone cannot change clinical trials, but with an optimal approach, it can correct their composition and correctly interpret the results [6]. As a result, the number of failed experiments can be reduced. The use of modeling is of particular importance at the stage of transition from the research part of drug production to the evidence-based part.

The purpose of the study is the development of mathematical and computer models for assessing the quality of technological processes for the preparation of medicines.

The following scientific results were presented as a part of the study:

– simplified scheme of the drug production technological process;
– functional models of drug technology quality control processes;
– mathematical model of the quality of the medicines manufacture;
– algorithm for evaluating the quality of medicines;
– computer model of the quality indicator of the drugs manufacture "SapaDari.exe".

Practical value of the research: in this article, a mathematical model has been developed that calculates a comprehensive indicator for assessing the quality of the technological process of manufacturing the drug "Atenolol" in a tablet form through experimental studies, which allows to improve the quality management of the drug production technological process.

Description of the technological process of the medicines manufacture

The complete technological process of tableting medicines consists of three stages: Preparation of materials for compaction; compaction of tablets; coating of tablets with a shell. When conducting intra-pharmacy quality control of medicines manufactured in a pharmacy, as well as homeopathic medicines, it is determined by a set of indicators that give a complete characteris-

tic of medicines [3].

To assess the quality of medicines manufactured in a pharmacy, two terms are used: "satisfactory" ("suitable product"), "unsatisfactory" ("unsuitable product").

The term "unsatisfactory" is used in case of non-compliance of the drug with one of the following parameters: characteristics (appearance, color, smell); transparency and color; decomposability; uniformity; absence of visible mechanical impurities in liquid preparations; authenticity of the record; deviations from the registered volume or mass, total volume (mass), total mass of individual doses and their quantity, the mass of individual medicines from the registered dose; indicator of acid-base balance; density; sterilization; microbiological purity, tightness of plugs; registration of the drug for release. The prepared preparations are subject to withdrawal and disposal if they are recognized as "unsatisfactory" ("invalid") as a result of intrapharmacy control.

The main goal of the pharmaceutical industry is to provide consumers with high-quality medical products. Despite the fact that their quality is controlled by both manufacturers and state certification bodies, it is quite possible that drugs that do not meet the quality requirements of medicines will enter the consumer market [7]. Such drugs can not only help a person, but also harm his health.

The production of drugs is a complex multi-stage, many hours of energy process, consisting of the following stages: measurement of components; screening; powder mixing; softening, mixing; granulation; drying; grinding, mixing; compression; dedusting; detailed measurement and packaging [4].

A simplified diagram of the technological process for the production of drugs in tablet form is shown in Figure 1.

The following designations are used in the above drawing: T – drying temperature, °C; – drying time, min; P – sealing pressure.

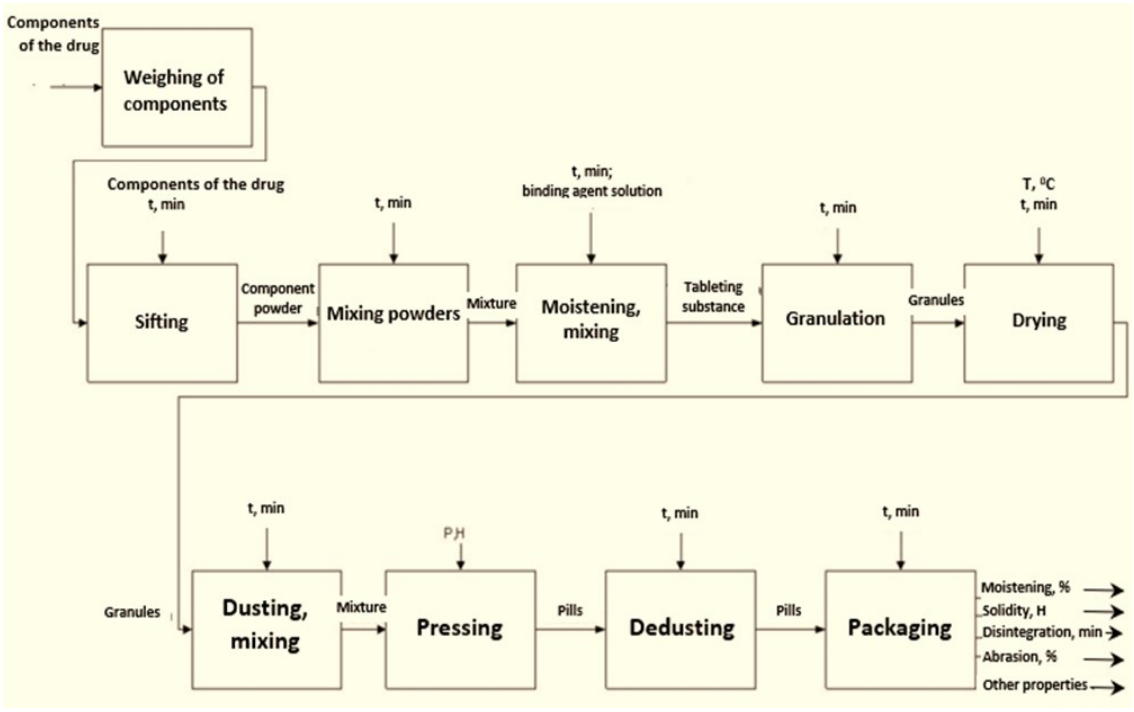

Figure 1. Simplified scheme of the technological process to produce drugs

Creation of functional and information models of the quality control system for the manufacture of medicines

Using the IDEF0 methodology, a model of the technological process to produce drugs in tablet form was developed. IDEF0 is a functional modeling methodology. The IDEF0 graphical language is very simple and compatible. Using the well-known graphical language IDEF0, the desired system is presented to developers and analysts as a set of interrelated functions. As usual, IDEF0 modeling is the first step in studying any system [8].

The quality indicators of the finished product are formed at each stage of production, but the most important stage in this technological chain is the drying stage. At this stage, quality indicators, such as moistening, are formed, and the main quality indicators of other preparations, such as strength, decomposition, grinding, etc., depend on this indicator.

To reduce the risk of obtaining low-quality medicines, it is necessary to create a mathematical model of each quality indicator and use the resulting model to predict quality in conditions of uncertainty of the production process. Organizational structures have a great influence on the definition and implementation of business processes. BPwin supports a clear definition of roles that defines and classifies the tasks or functions that make up business processes [9]. BPwin is used to build organizational charts based on user-defined roles. The functional model of drug production technology is shown in Figure 2.

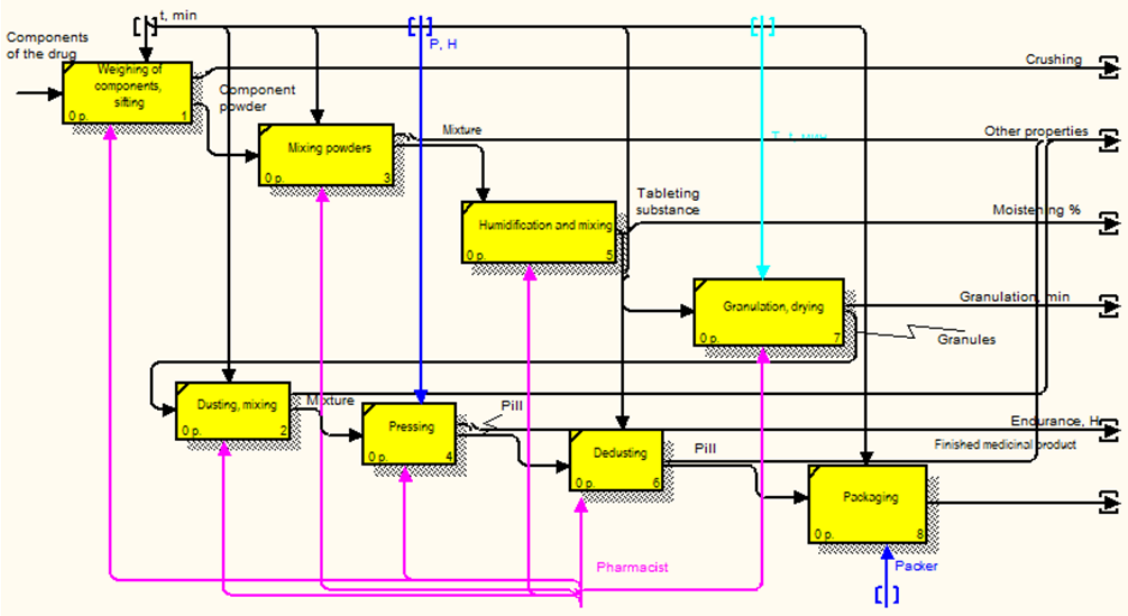

Figure 2. Functional model of drug production technology

Construction of a mathematical model of the manufacturing medicines quality.

The quality of medicines is the quality of medicines in accordance with state standards [10]. The quality standard of medicines is a regulatory document approved by the Ministry of Health of the Republic of Kazakhstan, consisting of a list of metered indicators and methods of quality control of medicines.

A correlation method was used to construct a mathematical model of the quality of medicines [11].

Unlike functional dependence, in statistical dependence, the random variables x and y are in-

fluenced by several random factors (which may be common to both). If the average value of the second value changes from a change in one value, then the statistical dependence is called a correlation dependence [12].

Correlation relations are static, since the value of the function y is not completely determined by the independent value of x. They arise between random variables when they are stochastically related to each other, when there are common random factors affecting the first and second variables that are not the same for both variables. Also, the relationship between the dependent variable y and the independent variable x is visible when each value of y corresponds to a random value of y, but when x changes, these values naturally change their positions.

In the simplest case, correlation analysis is used to determine the relationship between two indicators, one of which is an independent indicator x-factor, and the other is an independent indicator y. This dependence is characterized by the function $y = f(x)$ [13].

If the x and y coordinates are close to some curve in the correlation region, then a curvilinear dependence may occur.

To apply the obtained correlation to analysis and planning, it is necessary to determine the strength of the relationship between the two indicators. To do this, calculate the correlation coefficient (for linear functions) and the theoretical correlation dependence (for curvilinear functions). According to the obtained value, which can be from 0 (no connection) to 1 (there is a complete functional connection), a decision is made to apply the obtained regularity.

The work was carried out on the basis of reliable experimental data of the drug "Atenolol". The entire sample was divided into two parts. With the help of the first part (86 points), a mathematical model of the quality indicator was obtained, and after the technological process, the second part of the experimental data (16 points) was obtained, used to verify the accuracy of the obtained model. The main quality indicators of this drug and the parameters of the technological process of its production are given below [4]:

X1 – drying temperatures, C;
X2 – drying time, min
X3 – manufacturing coefficient;
Y – moistening, %;
Y1 – strength, H;
Y2 – decay, min;
Y3 – crushing, %;
Y4- integrity, %;
Z is a complex quality coefficient.

The final quality of the drug is determined by the complex quality indicator Z, which takes values from 0 to 1.

Z= {0; 0,09} – drug with a defect;
Z= {0,09; 1} – the drug meets all quality standards.

The value of this indicator determines whether a series of drugs is on sale or is assessed as defective. To find a connection between the parameters used, the value of the double correlation coefficient was found, tested using the student's criterion [14,15]. As a result, the following (1) dependencies were identified:

$$\begin{cases} Y = F(X_1, X_2); \\ Y_1 = F(Y); \\ Y_2 = F(Y); \\ Y_3 = F(Y); \\ Y_4 = F(X_3, Y); \\ Z = F(Y, Y_1, Y_3, Y_4) \end{cases} \quad (1)$$

The regression analysis method was used to find the types of functions for these dependencies and tested these models for adequacy using the Fisher criterion. The accuracy of the prediction was calculated using the average approximation error, i.e., according to the following formula (2):

$$\varepsilon^* = \frac{1}{n}\sum_{t=1}^{n}\frac{|y_t - y_t^*|}{y_t} * 100\% \quad (2)$$

where: yt – the actual value of the attribute; y_t^* – predicted value of the attribute; n – length of the time series.

As a result of the work carried out, the following models of drug quality indicators were obtained (3):

$$\begin{cases} Y = 9{,}79 - 0{,}11X_1 - 0.0212X_2; \\ Y_1 = 51.07 + 6.27Y; \\ Y_2 = 2 + 1.5Y; \\ Y_3 = 99.96 - 0.59Y; \\ Y_4 = 0.51X_3 + 0.13Y; \\ Z = -0.24 + 0.15Y + 0.54Y_4 \end{cases} \quad (3)$$

Thus, a mathematical model of the drug quality indicator has been obtained.

Construction of an algorithm for assessing the quality of manufacturing drugs.

An algorithm has been developed to assess the quality of manufacturing medicines. This algorithm consists of the following steps. When evaluating, the raw materials are considered first. The received raw materials are being tested. After the inspection, there is a process divided into two directions, called indicators of the quality of raw materials and raw materials. The raw material participates in the technological process of a particular production and is further divided into two directions: the drug and the parameters of the technological process in the flow. And raw material quality indicators are included in mathematical forecasting models. It is possible to obtain predictive values from mathematical models and check the adequacy of models with these values [4].

The adequacy of the model is checked to determine the suitability of the model. Figure 3 shows an algorithm for evaluating the quality of manufacturing medicines.

That is, it is divided into two directions, one is “yes”, and the other is “no”. If the direction "Yes" is selected, the predicted Z will be obtained. Then the adequacy of the model is checked. Two conditions for the adequacy of the model are obtained - “yes” and “no”. If the model is adequate, i.e., "yes" is selected, z<0.9. Here, if z<0.9 is satisfied, then the process returns to the choice of parameters.

Next comes the transition to the technological process of production, so the cycle repeats. And if the value of z < 0.9 does not satisfy, i.e., if “no” is selected, then the decision is moved to the decision block, where further diagnostics of the equipment, re-checking the quality of raw materials, adjusting the technological chain, etc. are carried out. And if the model is inadequate, i.e., “no” is selected, then it proceeds to the stage of correction of mathematical models. Here mathematical models are studied on model parameters. Thus, the adequacy of the model is checked again, and the cycle continues. After receiving the drug, there is a stage of quality control of the drug [16]. Depending on these quality indicators, the adequacy of the models is checked. This is part of the prediction section. If the model is adequate, or vice versa, the above steps take place.

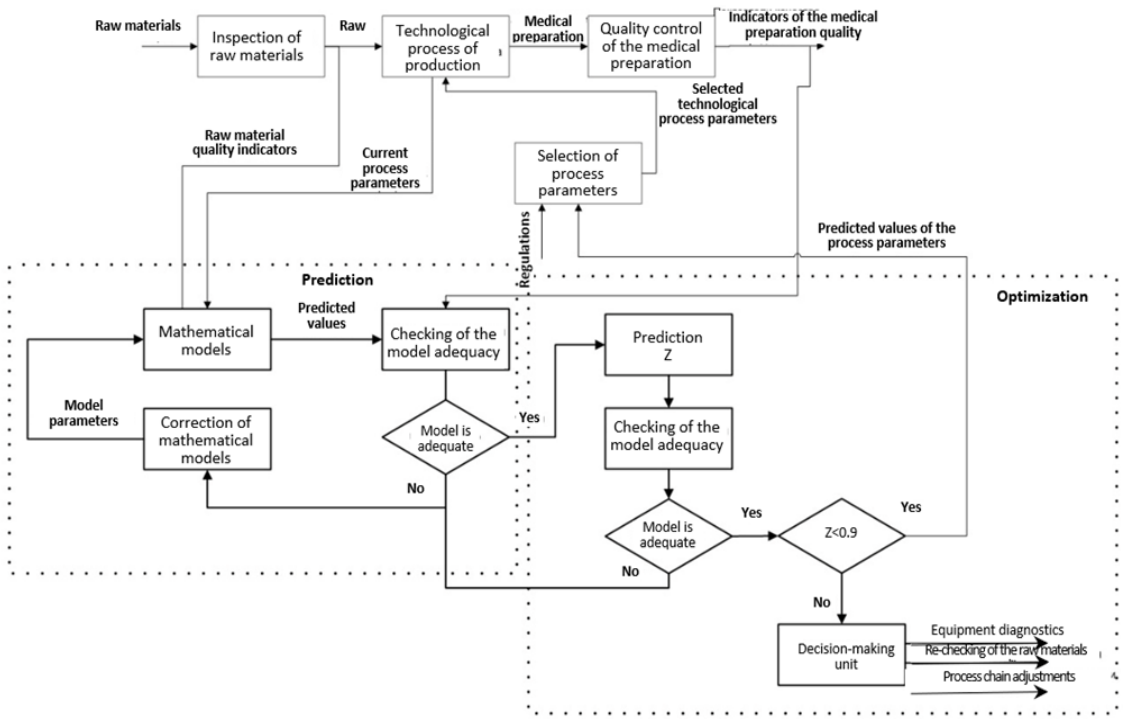

Figure 3. Algorithm for assessing the quality of manufacturing drugs

Creation of a computer model of the quality indicator for the manufacture of medicines

The “Main window” of the program consists of the menu “Database”, “Calculation”, “Queries”, “Reports”, “Help”, “Exit”. Consider the database menu in the main window. In the "Database" menu, you can access the database tables: "Drugs", "Composition of drugs", "TP parameters", "Pharmacists", "Composition units", "TP units".

In the "Queries" menu, you can open the following windows: "According to the composition of the MP", "Parameters of the MP manufacture technological process", "Average value of the complex quality indicator", "Pharmacists who created the MP" (Figure 4).

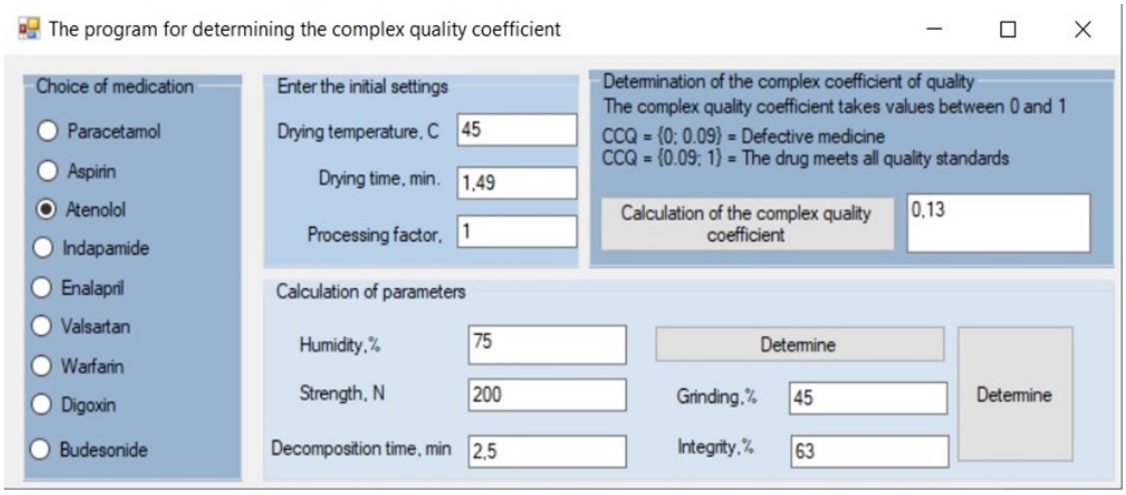

Figure 4. Window for calculating complex quality indicators

Conclusion. The production of medicines is a complex, multi-level, multi-hour process and consists of the following stages: weighing the components; sieving; mixing of powders; softening, mixing; granulation; drying; grinding, mixing; compression; dedusting, detailed weighing and packaging.

As part of the study, the technological process to produce the drug "Atenolol" in tablet form was studied, the main parameters of its technology were determined, and on their basis a mathematical model was built that calculates a comprehensive indicator of quality assessment. The relational database of indicators for assessing the quality of technological processes for the manufacture of medicines was designed in the SQL Server management system, and the computer model was created in the Visual Studio 2019 environment in C#. Mathematical and computer models built as a result of the study make it possible to increase the efficiency of quality control of the technological process of manufacturing medicines.

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