**Original Research**

# Optimal assessment share structured of Pharmacoeconomics for medical drugs according to minimax criterion

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### Abstract

**Objective:** To develop a comprehensive methodology for the optimal assessment of the share of the use of medicines, based on the procedure for ranking drugs according to the pharmacoeconomic point scale and the minimax criterion was applied. **Methods:** The author's approach is based on the minimax principle and allows solving the problem of optimizing the pharma drug portfolio based on available data, without the need to obtain the parameters of the Markowitz model associated with correlation analysis of data. **Results:** The authors obtained the optimal distribution of medicines in group A, B: 37% to 63%, which the authors consider a promising recommendation for a pharmaceutical company. The use of a similar approach, which does not contradict the Markowitz methodology, but allows us to reasonably accept the parameters of the model and give the optimal solution for the share distribution of drugs in medical practice. **Conclusion:** These mathematical tools, justified and equipped with an alternative confirmation, the minimax task can and should take a significant place in the complex pharma-analytical methodology of the management of large companies supplying concomitant drugs to the Russian and foreign market.

**Keywords:** pharmacoeconomic analysis; integrated point scale; integrated pharmacoeconomic threshold; income sharing; Australia's minimax criterion

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## INTODUCTION

An integrated pharmacoeconomic point scale assessment is an approach used for interpretation of the pharmacoeconomic analysis, where points are assigned or deducted depending on upward or downward deviations in the cost-effectiveness gradient values or budget of the assessed drug product against values of the comparative drug product. In the next phase, points assigned by the drug product are summed up and, if the result is below the minimum approved passing score threshold of the integrated assessment, the drug product is not included into the list of reimbursable drugs on its face. The starting point of the official introduction of the pharmacoeconomic analysis in the state system of preferential drug provision is August 28, 2014, when Decree of the RF Government No. 871 "On approval of Rules of forming of lists of medicinal preparations for medical application and the minimum assortment of medicinal preparations necessary for rendering of medical care" (onwards Decree No. 871) that for the first time had perpetuated the requirement for the pharmacoeconomic assessment in deciding upon inclusion of the drug products (DP) into the lists. The integrated point scale (scale) for the pharmacoeconomic assessment was developed and introduced and minimum threshold passing points (threshold) was introduced subject to this decree to enable consideration of DP for inclusion into the list. It should be noted that the approach implemented in Russia is a unique practical experience of use of so formal and rigid requirement for the pharmacoeconomic profile of DPs.[1-5] The amendments for Decree No. 871 were released and the aforesaid approach was changed significantly during 2018-2020.

For the healthcare system, it is important not only to have

a tool in the form of the presented criterion for including medicines in the reimbursed lists as separate healthcare technologies, but also approaches to determine the optimal uptake size of all available analogue technologies.[6] This need addresses to risk assessment of portfolio investments, that is one of the important tasks of risk management. The first ideas on the application of risk assessment indicators of a financial portfolio in order to reduce it by regulating the shares of assets that make up the portfolio were formulated by the American economist Markowitz in his article "Portfolio Selection" (1952) and applied in the securities market. Since then, the theory of portfolio investment has been intensively developing in various applied areas related to financial, technical and organizational decision-making. The expediency of solving optimization problems aimed at reducing portfolio risk under certain restrictions on profitability is explained by the need to make decisions about the structure of the investment portfolio.

The paper uses a model that fully replaces the Markowitz approach, in the absence of the data required for the Markowitz model, and is not a contradiction, in the presence of data. It is this model, based on the principle of minimizing the maximum weighted risk assessment in pharmaceuticals, with restrictions on the type of Markowitz model, that is presented in the work as an alternative to the multidimensional point-based assessment of the prospects of approaches to the use of medicines A, B, C, D. The authors hypothesize about balancing approaches tested by sound mathematical tools.

The next section provides key elements of the outdated and valid version of the document governing the use of pharmacoeconomic assessment results in deciding upon DP reimbursement as well as solution to determine optimal uptake size of the available (approved for reimbursement) medicines. Critical analysis of both versions of documents, established integrated pharmacoeconomic point scale assessment, and

proposed approach for optimal uptake is provided in the discussion section.

## METHODS

Procedure of the pharmacoeconomic assessment of DP for reimbursement that was introduced in Russia in 2014 required accounting of the cost analysis, budget impact analysis (BIA), and cost-effectiveness analysis (CEA). Key innovation was development of the point scale for assessment of DP and pharmacoeconomic assessment threshold. Pursuant to it, each type of analysis may assign certain number of points to DP (positive, if results are positive for DP, and negative, if pharmacoeconomic profile of DP is weak), following which such points are summed up. If point-based assessment of DP is not below +4, DP qualify for c reimbursement; if less than +4 points are assigned to DP, it could not formally qualify for reimbursement. Points for each type of pharmacoeconomic analysis are assigned as follows. The estimated market values of the studied DP and comparative DP were benchmarked during the cost analysis . Depending on how much market value of the studied DP is higher or lower (in percentage) than value of the comparative DP, - 10 points could be assigned to the studied DP if its market value by 100% exceeds value of the comparative DP and up to +8 points could be assigned if market value of the studied DP is lower than value of the comparative DP by over 80% (see Table 1). Similar approach was used for point-based interpretation of BIA results, except that indirect costs could have been accounted in BIA; total expenditures of the studied and comparative DP were benchmarked for the certain number of patients, and the range of points varied between -10 and +10 points. According to the scale, + 1 point (if the studied DP had preference) or -1 point (if the studied DP yielded to the comparative drug) could have been assigned to DP based on

Table 1. Qualitative assessment of the pharmacoeconomic effectiveness of DP subject to the outdated version of the Decree of the RF Government No. 871 dated 28.08.2014

| Assessment criteria | Assessment result | Percentage of deviation | Assessment scale (points) |
|---|---|---|---|
| 1. The presented cost of the course or annual treatment with the drug | Is higher than the cost of treatment with the comparative drug | 100 and more | - 10 |
| | | 80 - 100 | - 8 |
| | | 60 - 80 | - 6 |
| | | 40 - 60 | - 4 |
| | | 20 - 40 | - 2 |
| | | 10 - 20 | - 1 |
| | Is equal to the cost of treatment with the comparative drug | No more than 10 | 0 |
| | Is lower than the cost of treatment with the comparative drug | 10 - 20 | + 1 |
| | | 20 - 40 | + 2 |
| | | 40 - 60 | + 4 |
| | | 60 - 80 | + 6 |
| | | 80 and more | + 8 |
| Final points by the scale for assessment of presented costs | | | |

| 2. Advantages by the clinical and economic efficiency of the drug with regard to comparative drugs (for each of the studies presented or found independently) | Use of the DP reduces the overall costs (direct and indirect costs to be specified separately) for rendering medical care under the Programme on State Guarantees to Deliver Free Medical Care (budget impact) | up to 20 | + 2 |
| | | 20 - 40 | + 4 |
| | | 40 - 60 | + 6 |
| | | 60 - 80 | + 8 |
| | | over 80 | + 10 |
| | Use of the DP does not require increase of the overall costs (direct and indirect costs to be specified separately) for rendering medical care under the Programme on State Guarantees to Deliver Free Medical Care (budget impact) | | 0 |
| | Use of the DP requires increase of the overall costs (direct and indirect costs to be specified separately) for rendering medical care under the Programme on State Guarantees to Deliver Free Medical Care (budget impact) | Up to 20 | - 2 |
| | | 20 - 40 | - 4 |
| | | 40 - 60 | - 6 |
| | | 60 - 80 | - 8 |
| | | over 80 | - 10 |
| | Assessment of the costs and effectiveness (studied DP to comparative DP) | Decrease in value | + 1 |
| | | Increase in value | - 1 |
| The final points of the clinical and economic assessment of the proposal (at least + 4) for inclusion of DP into the lists | | | |

CEA results. Accounting of indirect costs was permitted during CEA. It should be noted, that the first version of the rules lacked information on how to determine the preference in terms of CEA – by comparison of the cost-effectiveness ratios (CER), by comparison of the incremental cost-effectiveness ratio (ICER) with "willingness to pay" threshold or otherwise (Table 1).

Having preserved the common concept of the pharmacoeconomic assessment of DP, the second version of the rules that emerged by the end of 2018 and passed through a number of amendments up to 2020 introduced a number of material changes in the procedure. First of all, the cost analysis results were no more accounted for in the pharmacoeconomic point scale assessment of DP. Secondly, point scale assessment methodology by CEA results was radically revised. In pursuance of this analysis, we have identified four different scenarios, which could be conventionally named as follows:

"Cost-effectiveness" analysis (when the studied DP is characterized by the clinical advantage and has the lowest CER). Depending on how far CER of the studied DP is below CER of the comparative DP, possible points varies between +6 and +10 (Table 2);

Incremental "cost-effectiveness" analysis (when the studied DP is characterized by the clinical effectiveness advantage, but has higher CER than the comparative DP). In this case, calculation of ICER for the studied DP and its comparison with ICER of the comparative DP out of the number of earlier qualified DPs is proposed. Within the scope of this scenario, assessment of the studied DP may bring between +1 and +9 points (Table 2);

Cost minimization analysis (CMA) (when clinical effectiveness of the studied DP and comparative drug is considered to be comparable). Within the scope of this scenario, between -8 and +8 points may be assigned to the DP (Table 2);

Table 2. Quantitative pharmacoeconomic effectiveness assessment of DP subject to the new version (dated 03.12.2020) of the Decree of the RF Government No. 871 dated 28.08.2014

| Assessment criteria | Assessment result | Deviation in percentage | Assessment scale (points) |
|---|---|---|---|
| 1. Clinical and economic assessment scale of DP | Clinical efficiency of DP is significantly higher than the clinical efficiency of the comparative drug | | |
| | Use of DP is characterized by lower costs than the comparative drug | over 60 | 10 |
| | | from 40 to 60 | 9 |
| | | from 20 to 40 | 8 |
| | | from 10 to 20 | 7 |
| | Insignificantly differs from the costs of the comparative drug | below 10 | 6 |
| | Clinical efficiency of the proposed DP corresponds to the clinical efficiency of the comparative drug | | |
| | Use of DP is characterized by lower costs than the comparative drug | over 60 | 8 |
| | | from 40 to 60 | 6 |
| | | from 20 to 40 | 4 |
| | | from 10 to 20 | 2 |
| | Insignificantly differs from the costs of the comparative drug | below 10 | 0 |
| | Is characterized by higher costs than the comparative drug | from 10 to 20 | -2 |
| | | from 20 to 40 | -4 |
| | | from 40 to 60 | -6 |
| | | over 60 | -8 |
| | Clinical efficiency of the proposed DP is significantly higher than the clinical efficiency of the comparative DP, and is characterized by higher costs than the comparative drug | | |

| | | over 60 | 9 |
|---|---|---|---|
| | ICER for the proposed DP is lower than ICER of the comparative drug | from 40 to 60 | 8 |
| | | from 20 to 40 | 7 |
| | | from 10 to 20 | 6 |
| | Is equal to ICER of the comparative drug | below 10 | 5 |
| | Is higher than ICER of the comparative drug | over 60 | 1 |
| | | from 40 to 60 | 2 |
| | | from 20 to 40 | 3 |
| | | from 10 to 20 | 4 |
| | Clinical efficiency of the proposed DP is significantly lower than clinical efficiency of the comparative drug | | |
| | Use of DP is characterized by lower costs than the comparative drug | over 60 | 1 |
| | | from 40 to 60 | 0 |
| | | from 20 to 40 | -1 |
| | | from 10 to 20 | -2 |
| | Costs insignificantly differ as regards to the comparative drug | Below 10 | -3 |
| | Is characterized by higher costs as compared to costs of the comparative drug | from 10 to 20 | -4 |
| | | from 20 to 40 | -5 |
| | | from 40 to 60 | -6 |
| | | over 60 | -7 |
| 2. Assessment scale of the DP impact on budgets of the budgetary system of the Russian Federation | Use of DP results in reduction of the direct medical costs | over 60 | 8 |
| | | from 40 to 60 | 6 |
| | | from 20 to 40 | 4 |
| | | from 10 to 20 | 2 |
| | Results in insignificant change of the direct medical costs | Below 10 | 1 |
| | Results in increase of the direct medical costs | from 10 to 20 | 0 |
| | | from 20 to 40 | -1 |
| | | from 40 to 60 | -2 |
| | | over 60 | -4 |
| The final points of the clinical and economic assessment of the proposal (at least + 6 for all drugs except orphan drugs with 2+ ) to qualify for inclusion of the DP in the lists | | | |

Finally, there is a scenario emerging in case when the studied DP is clinically less effective than the comparative DP (LowEf). Herewith, if DP is characterized by lower costs, it may bring up to +1 point, whereas if the studied DP is more costly (by over 70%) than the comparative DP, it could bring up to -7 points (Table 2).

It should be noted that both direct and indirect costs could be accounted for at implementation of all scenarios of the cost-effectiveness analysis. New version of the document accounts for the BIA results, however the range of point scale estimates was narrowed down to the range from -4 to +8 points (Table 2). Moreover, it was required to account only direct medical costs in BIA calculations. In the updated version of the document, pharmacoeconomic assessment threshold was increased from +4 to +6 points and obtained special threshold option for orphan drugs of +2 points (Table 2).

**Optimization of pharma solutions**

The solution to the problems of applying the minimax criterion and other approaches, as a result of which the parameters of the Markovitz model optimizing risk (taking into account profitability) are obtained, consists in introducing a new approach, in many ways similar to the Markovitz model (in the presence of risk parameters associated with the standard deviations of returns included in the portfolio of financing projects), and fully replacing such an approach with strict requirements: higher income - the risk is higher, taking into account those risk assessments that are adequate to the real practical interpretation of the solution (scores, ratings, probabilities of problems, and others). The author's approach is universal and promising. It does not deny historical principles, and allows you to take into account new technologies in the process optimization mode.

Let $\theta_i$ – unknown variable denoting the fraction $i-$ the drug for which the clinic's funds were released for the treatment of patients is in the portfolio of this clinic.

Denote $\theta = (\theta_1,...,\theta_n)$ – the vector of unknown proportions of the purchase and use of drugs (excluding expired drugs that have not found use, from which the effectiveness decreases). It is these components that need to be obtained as a result of solving the optimization problem. Risk assessments of the pharmaceutical products included in the portfolio (costs in US dollars) are denoted by $V_i > 0$, $i = \overline{1,n}$. The specified parameters are the input parameters of the model, their values must be calculated by the time the model is built.

As a risk assessment of the pharmaceutical portfolio, let's consider the maximum risk assessment of pharmaceutical drugs, taking into account their shares in the portfolio:

$$\Psi(\theta) = \max_{i=\overline{1,n}} V_i \theta_i \quad (1)$$

Since it is possible to refuse to receive higher returns only with the prospect of reducing risk, we consider

$$\eta_1 > ... > \eta_n > 0 \text{ и } V_1 > ... > V_n > 0.$$

So, in this formulation, it is required to diversify risks evenly ($V_i$) between all the pharmaceutical products that make up the portfolio, weighing them by shares in the portfolio, by choosing these shares of financing from n drugs that have a positive effect on the patient, but have side effects that symbolize risks.

$$\Psi(\theta) = \max_{i=\overline{1,n}} V_i \theta_i \to \min_{\theta \in \Omega}, \quad (2)$$

$$\Omega = \{\theta = (\theta_1,...,\theta_n) \in R^n : \sum_{i=1}^{n} \theta_i = 1, \sum_{i=1}^{n} \eta_i \theta_i = \eta_p \}. \quad (3)$$

Set (3) contains a requirement for the sum of the shares and an additional requirement for efficiency.

Results:

Let $J(\theta) = \{i \in \overline{1,n} : \Psi(\theta) = V_i \theta_i\}$.

It is not difficult to prove that they ate $\theta^* \in D$ is the solution of the problem (1)-(2) when

$$\eta_p \neq \left(\sum_{i=1}^{n}\eta_i V_i^{-1}\right) \Big/ \sum_{i=1}^{n} V_i^{-1},$$

$J(\theta^*) = \{1,...,n-1\}$, либо $J(\theta^*) = (2,...,n\}$.

Indeed, the function $\Psi(\theta)$ is convex on $R^n$.

In accordance with the fact from the convex analysis of the decision criterion $\theta^* \in D$ the task is to fulfill the ratio:

$0_n \in \partial\Psi(\theta^*) - K^+(\theta^*, D)$, где $0_n = (0,...,0) \in R^n$ (4)

$\partial\Psi(\theta)$ – subdifferential of the function $\Psi(\cdot)$ at the point $\theta$,

$K^+(\theta^*, D)$ – conjugation of the cone of possible directions of the set $D$ at the point $\theta$. Using the means of convex analysis, it is not difficult to establish that for $\theta^* \in D$

$\partial\Psi(\theta^*) = \boldsymbol{o}\left(\{0,...,0,\sigma_i,0,...,0\} : i \in I(\theta^*)\right)$ (5)

$K^+(\theta, D) = \{\theta = \lambda 1_n + \boldsymbol{\eta}, \lambda, \mu \in R\}$ (6)

Here $1_n = (1,...,1) \in R^n$, $\eta = (\eta_1,...,\eta_n) \in R^n$, $\boldsymbol{o}$ $A$ – convex hull of a set A. Substitution of formulas (4)-(5) in relation (3) and the assumption that the set $J(\theta^*)$ contains less than elements, immediately leads to a contradiction. And the assumption that $J(\theta^*) = \{1,...,n\}$ says that this is only possible if

$$\eta_p = \left(\sum_{i=1}^{n}\eta_i V_i^{-1}\right) \Big/ \sum_{i=1}^{n} V_i^{-1}$$

It remains to prove that the set $J(\theta^*)$ it consists of elements arranged in a row. Suppose the opposite, that is $J(\theta^*) = \{1,...,n\} \setminus \{i_0\}$, $i_0 \in \overline{2,n-1}$. Then from (3) - (5 follows the existence of numbers $\alpha_i > 0, i \in \overline{1,n} \setminus \{i_0\}$, as well as numbers $\lambda$ and $\mu$ from $R$, satisfying the system:

$$\alpha_1 V_1 - \lambda - \boldsymbol{\eta}_1 = 0, \cdots, -\lambda - \boldsymbol{\eta}_{i_0} = 0, \ldots,$$
$$\alpha_n V_n - \lambda - \boldsymbol{\eta}_n = 0, \alpha_1 + ... + \alpha_n = 1.$$

Solving this system, we get $V_i = \mu(\eta_i - \eta_{i_0})\alpha_i^{-1}$ for everyone $i \in \overline{1,n} \setminus \{i_0\}$. So if $1 < i_0 < n$, that $V_1$ and $V_n$ they take different signs, due to the ordering of numbers $\{\eta_i\}$, $i = \overline{1,n}$. This contradicts the condition of their positivity. The fact that there is a solution to the problem has been proved, an identification feature has been obtained, it remains to get a solution in the form of formulas that will find practical application.

**Reasonable formulas for optimizing the pharma portfolio according to the minimax criterion**

Suppose that: $v = \sum_{i=1}^{n} V_i^{-1}$, $\gamma = \sum_{i=1}^{n} \eta_i V_i^{-1}$, $\eta_p^* = \gamma/v$.

In relation to $\eta_p$, the solution of the problem (1)-(2) is $\theta^* = (\theta_1^*,...,\theta_n^*)$:

1)     when $\eta_p = \eta_p^*$, $\theta_i^* = 1(v\,V_i)$, $i = \overline{1,n}$.

2)     When $\eta_1 > \eta_p > \eta_p^*$, $\theta_i^* = \dfrac{\eta_p - \eta_n}{V_i(\gamma - \eta_n v)}$, $i = \overline{1,n-1}$,;

$\theta_n^* = (\eta_1 - \eta_p)/V_1 + ... + (\eta_{n-1} - \eta_p)/V_{n-1}(\gamma - \eta_n v)$

if $(\gamma - \eta_n/V_n)(v - 1/V_n) < \eta_p < \eta_1$, то $\theta_n^* < 0$.

3)     when $\eta_n < \eta_p < \eta_p^*$, $\theta_i^* = \dfrac{\eta_p - \eta_1}{V_i(\gamma - \eta_1 v)}$, $i = \overline{2,n}$,

$\theta_1^* = (\eta_2 - \eta_p)/V_2 + ... + (\eta_n - \eta_p)/V_n(\gamma - \eta_1 v)$;

if $(\gamma - \eta_1/V_1)(v - 1/V_1) > \eta_p > \eta_n$, then $\theta_1^* < 0$.

Proof. It is not difficult to show that the solution of the problem (1)-(2) exists. In accordance with the above fact, there are three possible options for the set $J(\theta^*)$:

$J(\theta^*) = \{1,...,n\}$, $J(\theta^*) = \{1,...,n-1\}$, $J(\theta^*) = \{2,...,n\}$,

which easily leads to unambiguous corresponding solutions and completes the substantiation of the mathematical profile problem.

Data analysis algorithm for solving the problem (1)-(2):

-       calculate values
$v = \sum_{i=1}^{n} V_i^{-1}$, $\gamma = \sum_{i=1}^{n} \eta_i V_i^{-1}$, $\eta_p^* = \gamma/v$,
-       compare values η and , η*;
-       calculate the components of the vector θ* = (θ1*,…, θn).

2. Computational experiment (Excel), Table 3.

**Software solution for the amount of funding**

The program for the distribution of the volume of project financing is intended for the shared distribution of financing in the portfolio of innovative projects based on the solution of the optimization problem. The data is analyzed and then an algorithm is implemented to determine the share of financing in a group of projects competing for investment, in terms of maintaining the required level of profitability for a group of projects and reducing the risk of financial losses. The program can also be used to solve a wide class of tasks for finding portfolio assets with a given yield. Programming language: Delphi 7.

The result of the distribution of the volume of financing of projects intended for the equity distribution of investments in the portfolio of innovative projects based on the solution of the optimization problem are presented in tables 4 and 5.

Optimization based on Table 6 with an average efficiency requirement of 100 and 60, that is, 80.

The initial share totaled 45.4% (drugs A and B). Preparations A and B in optimization mode: 13.73/31.76= 27% to 73%.

| Table 3. Computational experiment (Excel) | | | | | | |
|---|---|---|---|---|---|---|
| Indicator | **A** | **C** | **B** | **D** | | |
| Risks (costs) | 150 | 120 | 55 | 30 | | |
| Effectiveness (+) | 100 | 90 | 85 | 60 | | |
| of the Proportion of drugs | 0,137286 | 0,171606 | 0,374415 | 0,316693 | | |
| Limitation of the amount of shares | | | | | 1 | 1 |
| Limitation on the effectiveness of complex use of drugs | | | | | 80 | 80 |
| Goal | | | | | 20,5928501 | |
| Check: | 20,5928 | 20,5927 | 20,5928 | 9,50077 | | |

| Table 4. Computational experiment (Excel) | | | |
|---|---|---|---|
| **Indicator** | **Efficiency** | **Costs, USD** | **Optimization (for use)** |
| The investigated drug A | 100 | 150 | 13,73% |
| Comparison drug With | 90 | 120 | 17,16% |
| Drug D | 85 | 55 | 37,44% |
| Drug B | 60 | 30 | 31,67% |
| | | | 100,00% |

| Table 5. Optimization (A B) | | | |
|---|---|---|---|
| **Indicator** | **Efficiency** | **Costs, USD** | **Optimization (for use from two drugs A and B, from 45.4%)** |
| The investigated drug A | 100 | 150 | 27% |
| Drug B | 60 | 30 | 73% |
| | | | 100,00% |

| Table 6. Number of points (according to module) of each type of pharmacoeconomic analysis in the new version (dated 03.12.2020) of the Decree of the Russian Federation Government No. 871 dated 28.08.2014 | | | | | | |
|---|---|---|---|---|---|---|
| **Points** | **BIA** | **Pharmacoeconomic analysis (different scenarios)** | | | | **-** |
| | | **CEA** | **ICEA** | **CMA** | **LowEf** | **Summ** |
| **Sum max point** | 28 | 46 | 45 | 40 | 29 | from 57 to 74 |

## RESULTS

Short review of the first version of the document shows that various types of the pharmacoeconomic analysis were characterized by different weights on the scale: if cost analysis and BIA could bring up to +8 and +10 points, accordingly, (or deduct -10 points) in the point scale assessment of the pharmacoeconomic profile of DP, CEA may bring +1 point or deduct -1 point, accordingly. Weight of the said types of pharmacoeconomic analysis on the scale may be illustrated as a ratio between the number of (by module) points, which may provide each separate type of analysis, and the number of points of all three types of analysis (Table 7, Figure 1).

Evidently, if threshold value of the pharmacoeconomic assessment is +4 points, the results of costs analysis and BIA are decisive. Such allocation of weights for various types of analysis in the pharmacoeconomic assessment challenged the possibility of making positive decision regarding the reimbursement of the innovative DP, since majority of the innovative DP, which is characterized by better efficiency, at the same time requires more finance.[7,8] In pursuance of the introduced scale it meant that all advantages provided to the innovative DPs brought only +1 point. In the exceptional cases, additional points may be assigned based on BIA results, when innovative DP allowed significant reduction of the direct and indirect costs by prevention of complications.[9,10] (accounting of indirect costs was allowed in the first version of Decree No. 871 during BIA).

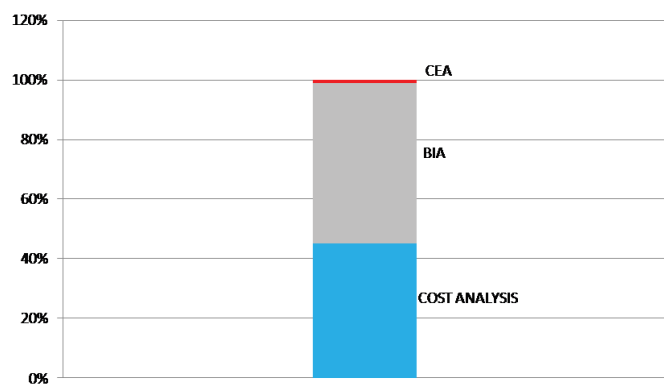| Table 7. Number of points points (by module) for each type of pharmacoeconomic analysis in the outdated version of the Decree of the Russian Federation Government No. 871 dated 28.08.2014 | | | | |
|---|---|---|---|---|
| **Types** | **Cost analysis** | **BIA** | **CEA** | **Sum** |
| **Sum max point** | 52 | 60 | 2 | 114 |



**Figure 1.** Allocation of weights for each type of pharmacoeconomic analysis according to the outdated version of the Decree of the Russian Federation Government No. 871 dated 28.08.2014

Practical experience of use of this document had confirmed the imbalance of the proposed scale and threshold for the pharmacoeconomic assessment.[11,12]

Paradoxical situations have emerged by deeper analysis of the pharmacoeconimic point scale assessment in the first version of the document: thus, if the examined innovative drug would have been characterized by the exclusive efficiency, for instance, added 1 QALY to a patient annually, and its costs would have been equal to the costs of obsolete comparative DP that is significantly less than the clinically efficient (added 0.0001 QALY per annum), then the innovative drug would have not been included into the lists since having got +1 point under the CEA it would have got 0 points based on the cost analysis and, assuming, +2 points based on BIA due to the insignificant reduction of the overall costs by prevention of the complications and the need for treatment, and, finally, have not got the required +4 points of the summary pharmacoeconomic assessment (+1+2+0 = +3 points) (Table 8).

The introduced rigid scale and threshold for the pharmacoeconomic assessment corresponds to the directorial formalized decision-making approach and minimizes the possibility of negotiations on the matter of concern.[13] From the other side, if the points allocation procedure for various types of pharmacoeconomic analysis was more transparent, the developed scale could have been treated as a successful experience of use of the multiple-criteria decision making analysis.

The introduced scale had forced the researchers to be more flexible in selection the efficiency criteria, accounting of the costs and comparative DP – faucets of the pharmacoeconomic assessment, which were left outside the strict requirements of the documents.[14] Professional community had repeatedly drawn the attention to the stated drawbacks in the effective rules and, thus, changes to the effective rules were officially adopted on 29.10.2018.

| Table 8. Example of the pharmacoeconomic assessment of DP subject to the outdated version of the Decree of the Russian Federation Government No. 871 dated 28.08.2014 – cost-effectiveness analysis (and budget impact analysis) | | |
|---|---|---|
| **DP A (examined drug product)** | **Technology** | **DP B (examined drug product)** |
| 1,000 | Effectiveness, QALY | 0,001 |
| 400 | Market value (cost analysis), USD | 400 |
| 600 | Total expenditures (budget impact), USD | 650 |
| Scoring by results of pharmacoeconomic analysis | | |
| Based on results of cost analysis | 0 | |
| Based on results of BIA | +2 | |
| Based on results of CEA | +1 | |
| Conclusion: examined DP gets +3 points on the scale, which is below the threshold +4 points, and, thus, formally it could not be recommended for inclusion into the lists | | |

According to Table 6, new version of the rules had provided for the allocation of points between different types of the pharmacoeconomic analysis towards the increase of the relative weights of the cost-effectiveness analysis (and its variants) in the pharmacoeconomic assessment. If in the first version of the document relative weight of the indicated type of analysis did not exceed 5%, it had been increased in the new version, depending on the type of analysis, from 51% to 63% (Figure 2).

With introduction of the new version, the above example (Table 6) could now get the following point scale assessment. Based on CEA results, being characterized by lesser CER than CER of the comparative DP, drug A gets from +6 to +10 points (in this case, +10) and, assuming, 0 points under BIA, since according to the new rules only direct medical costs shall be accounted. Cost analysis results do not contribute to the point scale assessment. Accordingly, DP A gets +10 points (+10+0 = +10 points) of the summary pharmacoeconomic assessment that exceeds the preset threshold value of +6 points, and may qualify for reimbursement.

Real effect of increase of the minimal assessment from +4 to +6 points on the possibility of overcoming such barrier by



**Figure 2.** Allocation of weights for each type of pharmacoeconomic analysis according to the new version of the Decree of the Government No.871

the examined DP was shown during its implementation into practice after 2019 and on the whole seemed, new threshold is affordable. It should be separately stated that there are no explanations on how to determine the threshold value.

## DISCUSSION

The updated version raised a number of methodological issues regarding the proposed vision of conduction of the

pharmacoeconomic analysis by authors of such document. It should be noted that new version of the rules was prepared by the profile agency headed by ISPOR member. The said agency had developed requirements for quality of the pharmacoeconomic studies. Key innovation of the document raising more issues was waiver of ICER comparison with "willingness to pay" threshold during the ICEA by replacing it by reference value of ICER of the comparative DP.[15-18] For the better understanding of this approach, it should be exemplified (Table 9, 10). If drug A is examined in the research; drug C is comparative DP, then subject to the new rules it is required to compare independently estimated ICER for the DP A and C. The rules require the use of the uniform efficiency criteria during calculation of ICER for the DP A and C, however it lacks any indications regarding the selection of drugs D and B (Table 10). Herewith, it is evident that selection of DP D and B has a great impact on the obtained ICER values (Table 10, example No. 1-2). There is also another interpretation of ICER comparison methodology: the estimated ICER of DP A and comparative drug C is compared with ICER of drug C and some "third-party" drug D (Table 10), where selection of drug D has also an express impact on ICER value (Table 10, Examples 1-2).

Besides, the inaccuracies in the methodology at description of ICER of the comparative drug and the proposed approach to use the ICER for the comparative DP as some reference value also raises some issues. Nevertheless, if "willingness to pay" threshold represents an aggregated value, methodology of which is reasonably criticized[19,20] then, in our view, the underlying principles of "willingness to pay" threshold concept are known and principles justifying the lawfulness of use of the separate point-based assessments (ICER of comparative DP) as reference values are unfounded. It should be noted that authors of this methodology, having criticized the "willingness to pay" threshold, had proposed to replace it by the estimated

### Table 9. First interpretation of ICER calculation methodology

|  | Efficiency | Costs | ICER |
|---|---|---|---|
| Examined drug A | $Ef_A$ | $Cost_A$ | $(Cost_A - Cost_B)/(Ef_A - Ef_B)$ |
| Drug B | $Ef_B$ | $Cost_B$ | |
| Benchmark drug C | $Ef_C$ | $Cost_C$ | $(Cost_C - Cost_D)/(Ef_C - Ef_D)$ |
| Drug D | $Ef_D$ | $Cost_D$ | |
| Example No. 1 | | | |
|  | Efficiency | Costs, USD | ICER |
| Examined drug A | 100 | 150 | |
| Drug B | 60 | 30 | 3 |
| Benchmark drug C | 90 | 120 | |
| Drug D | 85 | 55 | 13 |
|  | | | |
|  | Efficiency | Costs, USD | ICER |
| Examined drug A | 100 | 150 | |
| Drug B | 95 | 80 | 14 |
| Benchmark drug C | 90 | 120 | |
| Drug D | 85 | 55 | 13 |

### Table 10. Second interpretation of ICER calculation methodology and calculation examples

|  | Efficiency | Costs | ICER |
|---|---|---|---|
| Examined drug A | $Ef_A$ | $Cost_A$ | $(Cost_A - Cost_C)/(Ef_A - Ef_C)$ |
| Benchmark drug C | $Ef_C$ | $Cost_C$ | |
| Benchmark drug C | $Ef_C$ | $Cost_C$ | $(Cost_C - Cost_B)/(Ef_C - Ef_B)$ |
| Drug B | $Ef_B$ | $Cost_B$ | |
| Example No. 1 | | | |
|  | Efficiency | Costs, USD | ICER |
| Examined drug A | 100 | 150 | |
| Benchmark drug C | 90 | 120 | 3 |
| Benchmark drug C | 90 | 120 | |
| Drug B | 80 | 50 | 7 |
| Example No. 2 | | | |
|  | Efficiency | Costs, USD | ICER |
| Examined drug A | 100 | 150 | |
| Benchmark drug C | 95 | 80 | 14 |
| Benchmark drug C | 95 | 80 | |
| Drug B | 90 | 70 | 2 |

reference ICER, not for separate DPs, but for the aggregated ones for each pharmacological group (However, this provision was not included in the final version of the Decree No. 871).

Another issue of DP assessment under the new version of the Decree of the Russian Federation Government No. 871 is situation, where absence of the statistically significant difference between the examined DP and comparative drug was proven based on the effectiveness analysis results; however, in such a case, the examined DP is characterized by lower market value (CMA scenario). In terms of the healthcare system, c reimbursement of such DP would be accompanied by certain economy (at comparable level of efficiency), which, certainly, brings positive result. Evidently, the higher is value of saving, the more beneficial would be the use of the studied DP. However, in terms of decision making,[21] DP saving opportunity is decisive. This situation is considered in detail on example provided in Table 11; for illustration, in this example we only account for the direct costs of pharmacopeia. If the examined DP A, given its comparative efficiency, is characterized by savings in the amount of 19% (and recalculation of all population of patients for the absolute values in BIA may show significant savings) against the comparative DP B, it would not get the required minimum scoring (+ 6 points) on the scale and would not formally qualify for reimbursement.

Taking decisions on such algorithm may render negative impact on the development of competition at the pharmaceutical market and, accordingly, on the market assortment since, in fact, the document considers insignificant any reduction in price for the drug by less than 20% as opposed to the comparative drug. Such approach to reduction of the price is widely used at determination of prices for DP reproduced under one International Nonproprietary Name (INN) (when

| Table 11. Example of pharmacoeconomic assessment of DP according to the new version (dated 03.12.2020) – "cost minimization" scenario (and "budget impact" analysis) | | |
|---|---|---|
| DP A (examined drug) | Technology | DP B (benchmark drug) |
| 1,000 | Efficiency, QALY | 1,000 |
| 97 200 (savings 19% or USD 22 800) | Market value (cost analysis), USD | 120 000 |
| Scoring assessment based on results of pharmacoeconomic analysis | | |
| Based on CMA results | +2 (savings on drug A 19%) | |
| Based on BIA results | +2 (savings on drug A 19%) (transfer of 100 of patients from DP B to DP A would be accompanied by savings in amount of 2.28 mil. rubles; additional 24 patients could be treated with DP A out of such savings) | |
| Conclusion: the studied DP gets +4 points on the scale that is lower than the threshold of +6 points, and thus it could not be formally recommended for inclusion into the list. | | |

registration of each further reproduced drug is possible at significant reduction of price for such drug as compared to the reference drug), however pharmacoeconomic assessment is conducted in the majority of cases for the original DPs, various INN. Therefore, in this situation the producer, not being ready to reduce the price of its original DP by over 20% as compared to the alternative listed drug, may refuse of either listing its drug or its registration at the Russian pharmaceutical market.

We would like to draw attention on allocation of the points in the "cost-effectiveness" and ICEA scenarios. According to Table 2, CEA analysis may bring between +6 and +8 points, whereas ICEA may bring between +1 and +9 points. In our view, scenario of "cost-effectiveness" analysis (when more efficient DP has lower CER) characterizes DP qualitatively better than ICEA scenario (ICER is less than the accepted reference value), and, accordingly, the later may not bring so much points as the former.

Point scale approach in the first version of the document remained unchanged: depending on how the estimated pharmacoeconomic parameter of the studied DP differs in percentage from the comparative DP, the first one gets certain point (-7 points, -4 points… +1 point, +2 points… +9 points, +10 points). In terms of the methodology, such scoring raises a number of objections. First of all, having assessed the difference between the estimated parameters of the studied DP and comparative drug in percentage terms, we face possible errors/deviations in the assessments, since, as the case may be, 1% may comprise both 100 USD and 100000 USD in the absolute values. Even provided such limitation, it is acceptable to determine the extent of the difference between the BIA and CMA results and between the studied and comparative DPs, since results represent absolute values. It is hard to find the basis for expression of the extent of the difference between CER and ICER, in principle, and in % terms, in particular. Both CER and ICER represent specific values and have qualitative interpretation: conclusion on the pharmacoeconomic benefit of DP or its cost-effectiveness is drawn based on the information on whether it has lower CER or ICER values not exceeding its reference values, and, in such a case, it is not critical to what extent such values are lower (provided that the results pass sensitivity analysis). Accordingly, allocation of points for CEA (ICEA) appears to be irrelevant in principle, and for BIA

– poor informative, due to presentment of the difference in percentage terms.

Having summarized the results of our analysis, we could declare that new version of the document, from the one side, provides methodology of assessment according to the needs upon consideration of the innovative DPs, having increased the relative weight of CEA. However, at the same time, innovations require explanation of the following provisions:

What is the reason for comparison of ICER of the examined DP with ICER of the comparative DP; how to select the comparative DP at calculation of each ICER? The mathematical approach revealed the feasibility of using a comprehensive methodology.

Could DPs, assessed in the scope of CEA and ICEA, get one and the same points? The points will depend on the approach, different initial characteristics of risk (costs) and income (efficiency) drugs will receive an assessment adequate to the requirements of the investor (owner), he can change the requirements for the profitability of the portfolio.

Is it proper to build scale based on the percentage gradient of differences between the pharmacoeconomic values of the examined and comparative DPs?

The authors proposed two methods and obtained results according to which the use of drug A should be less extensive than the use of drug B, both methods indicate such a solution to the problem. The minimax approach gives a clear shared distribution of drug costs, optimal according to the methodology of the task justification.

**Software solution for drugs using new technological solutions, new solutions F, E have been added.**

After making a decision to preserve the life and health of patients, new methods should be added to stabilize the use of drugs, possibly the cancellation of drugs for damage to health. New approaches have been implemented. In the first (E), the doses of drugs were increased, in the second (F) a complete rejection of 50% of the drugs used. The patient didn't know about it. It must be said that the general methodology has shown the balance of treatment and the possibility of complete (or partial) refusal of medicines by the patient, without any damage to his health and active longevity.

To obtain such conclusions, a software device was needed. The author's program is designed to form a strategy for the implementation of the functional purpose and the mode of optimizing the use of drugs by patients in the selected clinical and procedural mode. The authors obtained the optimal distribution of drugs by zones of responsible use. The authors suggest that the technique will be implemented in the practice of emergency diagnostics and emergency medical care for patients with health problems within six months.

Scope of application, functional purpose: decision-making on orders of medicines in the system of a balanced approach to the treatment of patients, formation of a strategy for implementation in the mode of optimizing the use of drugs by patients in the selected clinical and procedural mode, optimization of the share distribution of drugs in the areas of responsible use using a minimax approach.

Program listing, code test & results (figure 3-figure 5).

```java
Package com.company;

//'main' method must be in a class 'Rextester'.
//openjdk version '11.0.5'

import java.util.*;
import java.lang.*;

public class Main
{
    public static void main(String args[])
    {
        Treatment t = new Treatment();
        System.out.println(
                t.res_e+" "
                +t.res_d+" "
                +t.res_f+" "
                +t.res_c+" "
                +t.res_b+" "
                +t.res_a);
    }
}

class Treatment
{
    double E_TOFACITIINIB = 125323;
    double D_ADALIMUMAB = 128495;
    double F_SARILUMAB = 133117;
    double C_GOLIMUMAB = 450835;
    double B_TOULIZUMAB = 590764;
    double A_BARICITINIB = 634105;

    double sumOfTreatment =
E_TOFACITIINIB+D_ADALIMUMAB+F_SARILUMAB+C_GOLIMUMAB+B_TOULIZUMAB+A_BARICITINIB;

    double subtraction_e = 5;
    double subtraction_d = 12;
    double subtraction_f = 11;
    double subtraction_c = 24;
    double subtraction_b = 5;
    double subtraction_a = 2;

    double sumOfSubstruction = subtraction_e + subtraction_d + subtraction_f +
subtraction_c + subtraction_b + subtraction_a;

    public double min_c (double a, double b, double c, double d, double e,
double f)
    {
        double x;
        return x=Math.min(f,Math.min(e,Math.min(d,Math.min(c,Math.min(a,b)))));
    }

    public double max_c (double a, double b, double c, double d, double e,
double f)
    {
        double x;
```

**Figure 3.** Program listing constraint by Java v. 13.0

```
class Treatment
{
    double E_TOFACITIINIB = 125323;
    double D_ADALIMUMAB = 128495;
    double F_SARILUMAB = 133117;
    double C_GOLIMUMAB = 450835;
    double B_TOULIZUMAB = 590764;
    double A_BARICITINIB = 634105;
```

**Figure 4.** Code testing data at figure 1



```
"C:\Program Files\Java\jdk-13.0.2\bin\java.exe" "-javaagent:C:\Program Files\JetBrains\IntelliJ IDEA Community
11.235847000650978 11.208721010021696 11.169428704394207 9.000561601454235 8.291474386394915 8.093967297083973
```

**Figure 5.** Results by running the program, allocated at figure 1

## CONCLUSIONS

Unlike the existing international practice, the system of pharmacoeconomic assessment of DPs was formed in Russia and continues to develop upon taking decision on DP reimbursement based on the strict scale with minimum formal passing point threshold. Based on the critical analysis, both positive changes in the evolution of pharmacoeconomic assessment procedure as well as a number of provisions requiring changes for further enhancement of this system were found.

Based on the author's approach adapted to optimize the systematic administration of drugs, factorial and stabilization signs of the risk structure of the process are analyzed, computational experiments are carried out. The authors have improved the point scale of calculation of drugs at the expense of software and optimization models. The authors are confident in the high prospects of the methodology. This conclusion is confirmed by the results of experiments that have shown high visibility and reliability of the results verified by software calculations.

The methods presented are as follows.

Firstly, during the data analysis, the authors applied a procedure for ranking medicines on a pharma-economic point scale and a minimax criterion. The complex application of these techniques was performed for the first time.

Secondly, the software for calculations on the share structure of the use of drugs has been performed. Such a solution is performed by a software module adapted to indicators and mathematical apparatus.

Thirdly, testing was performed and conclusions were obtained about the correct and reliable distribution of drug dosages. For this purpose, testing drugs that are safe for the patient's health were used. Their use did not show a significant role of the accepted modifications. This indicates the high stability of the author's model in the formation of the share structure of the use of drugs.

The implementation and testing of the new methodology in the practice of clinical diagnostics has shown high results. These include a full-scale and preliminary discussion of recommendations before the stage of exacerbation, which leads to timely treatment of patients without selecting the optimal dosages of drugs.

It is necessary to take into account the significant difference between the author's approach and the previous share distributions of drugs, the purpose of which was not to treat the disease, but to minimize the risks of using the drugs themselves. In the recommended system of drugs, changes relate to the scope of use and the scheme of implementation of treatment of patients. The system is very flexible, immediately reacts to new signals when the source data changes.

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The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

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