Doctoral School in Medical Sciences

Manuscript
CZU: 615.1/.2:34

BULIGA Valentina

LEGISLATION AND MANAGEMENT REFERENCES OF PHARMACEUTICAL SECURITY

316.01 - Pharmacy

PhD Thesis Summary
PhD Thesis in Pharmaceutical Sciences

Chisinau, 2019

The thesis was elaborated within *Vasile Procopişin* Social Pharmacy Chair
of *Nicolae Testemitanu* State University of Medicine and Pharmacy
of the Founding Consortium of the Doctoral School in the field of Medical Sciences.

Scientific leader:

Safta Vladimir, MD, Dr Habilitatus,
PhD in Pharmaceutical Sciences, Professor

Members of the guidance committee:

Brumărel Mihail,
MD, PhD in Pharmaceutical Sciences, assoc. prof.

Adauji Stela,
MD, PhD in Pharmaceutical Sciences, assoc. prof.

Spinei Larisa, MD, Dr Habilitatus,
PhD in Medical Sciences, Professor

The thesis will be held at 18.04.2019, 14.00 in *Nicolae Testemitanu* SUMPh, 165 Ştefan cel Mare şi Sfânt str., office 205 at the meeting of the Commission for public PhD thesis defense, approved by the decision of the Scientific Council of the Founding Consortium of 26.02.2019 (*Minutes no. 1*).

Commission for public PhD thesis defense:

President:

Valica Vladimir, MD, Dr Habilitatus,
PhD in Pharmaceutical Sciences, Professor

Members:

Safta Vladimir, MD, Dr Habilitatus,
PhD in Pharmaceutical Sciences, Professor

Diug Eugen, MD, Dr Habilitatus,
PhD in Pharmaceutical Sciences, Professor

Remiș Vladimir, MD, Dr Habilitatus,
PhD in Pharmaceutical Sciences, Professor

Nstreanu Anatolie,
MD, PhD in Pharmaceutical Sciences, Professor

Adauji Stela,
MD, PhD in Pharmaceutical Sciences, assoc.prof.

Lupu Mihail,
MD, PhD in Pharmaceutical Sciences, assoc.prof.

Author
Buliga Valentina

CONCEPTUAL REFERENCES OF RESEARCH

Up-to-dateness and importance of theme

Currently the pharmaceutical system of the Republic of Moldova faces a multitude of problems, such as:

- a drastic decrease in the quality of pharmaceutical services by involving non-specialists in the exercise of pharmaceutical activity;
- a reduced physical accessibility caused by the disappearance of vital medicines on the pharmaceutical market, as well as economic accessibility as a result of the imperfect pricing mechanism for medicines;
- ignoring and violating the demographic and geographical norms regarding the location and expansion of community pharmacies (situation tolerated until the modification of the licensing process of pharmaceutical activity – 27.10. 2017);
- a continuous increase of the shadow pharmaceutical market as a result of the imperfect automated mechanism for the circulation of medicines, the emergence of „online pharmacies", the illegal import of absent medicines on the pharmaceutical market, including counterfeit and falsified medicines;
- passivity and indifference of the Moldovan Pharmacists' Association regarding the problems the pharmaceutical system faces and others.

Given the existence of these and other issues, the necessity of scientific argumentation of the notion of pharmaceutical security as well as measures for identifying and preventing the potential dangers, which may affect the security, became logical and current.

Some issues of pharmaceutical security have been studied in scientific works carried out by H. Bale, 2017; T.I. Roberts, 2016; E. Walter 2012; И.С. Anosov, 2016; Д.В. Parkommenko, 2005 et. al., but no integral scientific work addressing this issue from a systemic point of view is found in the literature.

Description of the background in the research field and identification of research issues

The pharmaceutical system, as a component part of the health system, contributes directly to the achievement of the ultimate goal of the healthcare system by providing the medication process of each individual with the necessary medicines and pharmaceuticals: effective, harmless, consistent and accessible quality.

To achieve this goal, the Republic of Moldova assumes responsibility for ensuring a multidimensional national security, including pharmaceutical security. Thus, the importance of the researched problem results from the significance of human health protection.

It should be noted that no comprehensive research has been carried out so far on state pharmaceutical security.

The purpose of the scientific work is to develop the theoretical and practical argumentation of the Moldovan pharmaceutical security system.

General objectives:

- to argue theoretically and scientifically the term "pharmaceutical security", applying the systemic approach principles;
- to highlight the scope of pharmaceutical security at various levels: global, regional, national;
- to elaborate the methodical arsenal in order to quantify the characterization /influence factors of the pharmaceutical security and risk factors;
- to estimate the de facto state of the pharmaceutical security in the Republic of Moldova;
- to argument the recommendations aimed at strengthening the pharmaceutical security

management in the Republic of Moldova;

- to elaborate the concept and functionality of the pharmaceutical security system at various hierarchical levels in the Republic of Moldova.

The research methodology is based on the systemic approach and its derivatives: analysis and synthesis, study of factors and processes, current and follow-up analysis, system decomposition and construction, legislation analysis, argumentation and elaboration of draft legislation, strategies, and programs.

Scientific novelty

The scientific work, for the first time:

- investigates the multi-dimensional pharmaceutical security applying the systemic approach principles;
- develops a complex method of quantification of factors influencing the pharmaceutical security;
- argues and elaborates the concept of a new subsystem of the pharmaceutical system - the pharmaceutical security system.

The important scientific problem solved:

- the necessity of ensuring a continuous and functional pharmaceutical security subsystem has been demonstrated;
- current issues affecting the pharmaceutical security were highlighted as well as risk factors to be considered;
- decision matrix on ensuring the functionality of the pharmaceutical security system was worked out and the functions and conditions for securing the pharmaceutical security at the hierarchical levels in the Republic of Moldova were allocated.

The theoretical significance of the research lies in the theoretical argumentation of a new subsystem of pharmaceutical system, namely the pharmaceutical security. The systemic approach was complemented by two specific methods adapted to the purpose of determining the influence of factors on pharmaceutical security and the legislative coverage of ensuring the security of the domain.

Applicative value of the research work:

- a contribution to strengthening pharmacists training in pharmaceutical safety issues;
- amending and completing the pharmaceutical legislation of the Republic of Moldova in order to create and ensure a good functionality of the pharmaceutical security system as part of the pharmaceutical system;
- elaboration of the hierarchical staging of the implementation process of the total quality management of pharmaceutical services for application in pharmacies.

The main results forwarded to support

1. Situation regarding the pharmaceutical security at global, regional (EU) and national levels (Republic of Moldova).
2. Classifying and determining the influence of factors on pharmaceutical security.
3. Determining the degree of legislative coverage of the provision of pharmaceutical security in the Republic of Moldova.
4. Model of ensuring Pharmaceutical Security in the Republic of Moldova at three hierarchical levels: national, organizational and professional.

Implementation of scientific results

1. Amending and completing the Decision of the Parliament of the Republic of Moldova no. 153 of 15.07.2011 to approve the National Security Strategy of the Republic of Moldova by Parliament Decision no. 269 of 07.12.2017, point 4.5. „Improving the demographic situation,

population health and ensuring pharmaceutical security". (Project Promoted and Adopted – Official Gazette no. 441-450/755 of 22.12.2017).

2. Elaboration and promotion of the Draft Law on the modification and completion of some legislative acts (Laws: No. 1456 of 25.05.1993, no.1409 of 17.12.1997, no. 589 of 22.09.1995, no. 411 of 28.03.1995). (Draft Law and Informative Note; Law adopted The Official Gazette no. 1-5 of 04.01.2019).
3. Recommendations on strengthening the effectiveness of pharmaceutical system functioning aimed at achieving the final goal of the health system. (Implementation Act).
4. Recommendations on completing the Curriculum of the discipline "Management and Pharmaceutical Legislation", approved as set out in January, 2019 (Implementation Act).

Approval of the results. Some research results were presented and discussed at:

- Annual scientific conferences „Medicine Day at INF", Chisinau, 2003, 2004;
- Sixth Congress of Pharmacists of the Republic of Moldova, Chisinau, 2009;
- Scientific conference with international participation „From drug design to quality and harmlessness" in memoriam Professor Filip Babilev „80 Years from Birth", Chisinau, 2016;
- Scientific Conference with International Participation „Ethics Pharmacy: History, Realities and Perspectives" in memoriam Vasile Procopişin - Patriarch of Moldovan Pharmacy, MD-Dr. Hab., PhD. Pharm. Sciences, prof., and Nadejda Ciobanu – MD, PhD Pharm. Sciences, assoc. prof., Chisinau, 2018;
- Scientific-practical conference and meeting of the Republican Council of PhARM "Principles and directions of modern pharmacy development ", Chisinau, 2018.

Publications. The research theme was reflected in 12 integral articles and 4 dissertation theses, including 7 articles published during the doctoral school training at *Nicolae Testemitanu* SUMPh.

Volume and structure of the thesis. The thesis is elaborated according to the complex traditional type, exposed on 124 pages and contains: introduction, 4 chapters, each chapter containing 4 subchapters, general conclusions, recommendations, bibliography with 162 references. Annexes in 11 are displayed on 27 pages. Iconography includes 20 tables and 13 figures displayed on 22 pages (25% of the volume of the base thesis part).

Key words: systemic approach, system, pharmaceutical security, influence factors, management, quality.

The positive opinion of the Research Ethics Committee (Protocol no. 63 of 03 June 2016) was obtained.

THESIS CONTENTS

1. THEORETICAL AND EVOLUTIONAL FEATURES OF PHARMACEUTICAL SECURITY

The notion of security is defined as "the state of being free from any danger or threat; the feeling of confidence and quietness due to the absence of any danger" (explanatory dictionary).

In the literature, along with general notions, there are various sectorial approaches to security, such as military, political, economic, social security, etc. [11].

Currently, the notion of pharmaceutical security (PhS) is used to signify different issues that need to be solved in different countries:

- preventing the placing of falsified, counterfeit and low quality medicines on the pharmaceutical market;
- ensuring the security of medicines by strengthening clinical research and pharmacovigilance;
- ensuring adequate storage of medicines in pharmaceutical companies;
- minimizing the country's dependence on the import of medicines from other countries and development of the national pharmaceutical industry and others.

A major impact on the evolution of the global pharmaceutical industry as well as on the development of the pharmaceutical security concept has had a fair balance between the two components of the pharmaceutical industry goal:

- obtaining human health benefits;
- covering expenses and ensuring company profitability.

In cases where the pharmaceutical company is predominantly concerned with profitability to the detriment of health, the need for strengthening pharmaceutical security arises.

Multiple publications in this chapter are an eloquent demonstration of the current issues of pharmaceutical security.

The conditions in which the world pharmaceutical industry is developing today, as well as the trends for the future, suggest the need for further strengthening of pharmaceutical security at all levels – individual level - society, state - region - world, relying on the concept of human security.

The problems of pharmaceutical security are manifested at three levels: world - regional - national, being complementary and interdependent.

Among the wide range of global security pharmaceutical concerns counterfeiting is highlighted. According to the assessment of PSI President Harvey Bale, "there is no exact figure to assess the magnitude of the counterfeit drug phenomenon ... probably the range is 2%, but this small percentage distorts the real state of the problem: the US, EU, Japan, Canada - <0.2%; Russia – 10%; India – 15-20%; South East Asia – 5-10%; Latin America – 10-20%; Africa – up to 60% [1, 16].

The second major problem at international level is the theft of pharmaceutical goods. According to a report by the International Security and Monitoring Agency, theft of pharmaceuticals in the EU countries (in 2013), as a result of road transport hijack, amounted to about 116 million euros, while the Industry Council assumes that this figure tends to be grossly under-reported, which leads to a false perception of security [3].

At the regional level the European Union (in addition to issues related to the falsification of pharmaceutical products and their diversion into the supply chain), a major focus is on balancing the interests of pharmaceutical and public health sectors. In this context, the Council of Europe Parliamentary Assembly of 29 September 2015 urged the Member States to take concrete steps to improve the pharmaceutical industry interaction with health system actors [14].

In order to combat counterfeiting of medicines as well as to ensure supply chain security,

the idea of serialization of medicines is being promoted - assigning a unique identifier (number) for a packing unit - an identifier stored in a database together with some other information required in the product identification process [12].

In the Republic of Moldova, multiple issues affecting pharmaceutical security are highlighted through various sources of mass information: cartel arrangements, drug pricing, pharmaceutical market crisis, anabolic mafia, offshore pharmaceutical supply, illegal schemes with the involvement of pharmaceutical companies - being just some of the titles that „label" security.

2. ARGUMENTATION OF PHARMACEUTICAL SECURITY SYSTEM

The systemic approach is considered as a direction of the research philosophy and methodology, special scientific knowledge and social practice, underlying the research of objects as a system [25-27]. The analysis of the application of the systemic approach principles in the pharmaceutical field [8, 10] made it possible to highlight cases of incorrect application or non-observance of principles within the pharmaceutical system of the Republic of Moldova.

Systemic approach of pharmaceutical security

The analysis shows that in different countries researchers include multiple aspects in the notion of "pharmaceutical security": quality, security and efficacy of medicines, their transport and storage as required, accessibility and independence of import, their ethical development and promotion, rational use of medicines and so on. At the same time, analyzing the literature, it can be concluded that there is a lack of complex elucidation from the systematic approach of PhS notion and factors influencing state PhS ensuring.

In most cases, when tackling pharmaceutical security issues, counterfeit and falsified medicines, physical and economic accessibility of essential drugs, as well as compliance with ethical principles in the pharmaceutical industry and by health system actors, are highlighted to ultimately provide public health benefits.

Given the fact that PhS is a multifaceted and complex notion, it contains an ensemble of activities, processes, technologies, objectives, information, and entities, which all have an interfunctional, interorganisational and interpersonal interrelation.

Purpose is an important feature of any system [21]. PhS entails the following relevant formula of purpose: to provide a lasting state protection of the entire human community and every inhabitant against any threat (danger) resulting from the unsatisfactory / unlawful activity of the pharmaceutical system or its components [7].

According to the general theory of systems, any system is composed of "inputs", "contents", "outputs" and reverse link (feedback).

The Pharmaceutical Security System (PhSS) inputs, system contents and system outputs are shown in Table 1.

The analysis of the characteristics of pharmaceutical security system and pharmaceutical system allowed to highlight the following features:

- The PhSS contains the same components as the pharmaceutical system;
- The two systems are distinguished by the differences between "inputs" and "outputs", as well as the correlation between goals.

As a subsystem of the pharmaceutical system, PhSS is part of the medical system, which is a subsystem of the health system, all of which are part of an organized higher system, namely the social system.

Table 1. **Characteristics of the pharmaceutical security system**

Components	Description
Input	Norms, requirements, features, etc. established for products, activities, processes within the pharmaceutical system and other tangential systems.
Contents	The medicine: development, standardization, production, preparation, quality control, transportation, storage, distribution, promotion, pharmacovigilance, *enterprises*: laboratories, pharmaceutical plants, pharmaceutical stores, pharmacies, state bodies; staff; information; technologies; processes; activities, etc. [5].
Output	Providing the entire society and every person safety in terms of quality, efficiency and harmlessness of the products, activities and processes carried out within the pharmaceutical system.

Another important issue of pharmaceutical security is highlighting the PhSS correlation with the national security of the Republic of Moldova. It should be mentioned that no references to the pharmaceutical security were found in the National Security Strategy of the Republic of Moldova. Only certain threats, such as drug addiction, the spread of contagious diseases classified as "threats of social origin" are mentioned in the Strategy. At the same time, such threats as: absence of vital drugs, inaccessibility of medicines, falsified medicines on the pharmaceutical market, abusive promotion of ineffective medicines with a suspicious "safety", which necessarily had to be part of the National Security Strategy, initially, did not find any reflection in this important national policy document.

In order to remedy this gap, based on the results of the research, the National Security Strategy was complemented by the notion and content of pharmaceutical security.

The analysis and synthesis of PhSS components allowed highlighting the following three main directions that determine the pharmaceutical security in the Republic of Moldova:

I. ensuring efficacy, harmlessness and good quality of medicines;

II. ensuring physical and economic accessibility of medicines;

III. ensuring a good quality of all pharmaceutical services and a proper functioning of the entire pharmaceutical system.

Considering the three directions determining the pharmaceutical security, three groups of factors influencing and characterizing the pharmaceutical security system of the Republic of Moldova were elaborated:

I. Ensuring efficacy, harmlessness and good quality of medicines

1.1. conducting research on the development of medicines based on ethical principles aimed at obtaining health benefits;

1.2. proper and effective operation of the authorization procedure for the manufacture of medicines in domestic enterprises;

1.3. compliance with the requirements of good practice rules: laboratory (GLP), clinical studies (GCP) and manufacturing (GMP) of medicines;

1.4. ensuring the quality of drug substances and excipients used in the production and preparation of drugs;

1.5. proper and effective functioning of the pharmacovigilance service;

1.6. ensuring transparency of the research and development process in the field of new drug development;

1.7. ensuring efficiency of the authorization process (expertise, approval, registration) of the marketing of medicines;

1.8. ensuring the compliance and efficiency of the import authorization process;
1.9. preventing the placement on the pharmaceutical market of medicines not subject to quality control;
1.10. undertaking measures to prevent the placing of falsified and substandard medicines on the pharmaceutical market;
1.11. ensuring compliance (GDP, GSP) and Compliant Carriage (GTP) of medicines.

II. Ensuring physical and economic accessibility of medicines

2.1. uniform location of community pharmacies throughout the country, corresponding to the demographic and geographical standards;
2.2. ensuring the presence of essential drugs, including covered prescription medicines in:

- State Medicines Nomenclature;
- national catalog of producer prices;
- pharmaceutical warehouses;
- community pharmacies;
- medical-sanitary institutions (according to the institutional pharmacotherapy and national clinical protocols);

2.3. establishing responsibilities for the presence / absence of essential medicines on the pharmaceutical market;
2.4. developing and implementing the concept of orphan drugs;
2.5. ensuring day-to-day drug delivery and emergency care - over 24 hours;
2.6. ensuring information availability on the presence / absence of medicines in community pharmacies / pharmaceutical warehouses;
2.7. setting the requirement of minimum mandatory range of medicines in community pharmacies and pharmaceutical warehouses;
2.8. establishing a legal norm prohibiting the ungrounded refusal of medicines delivery from the pharmaceutical warehouses to pharmacies and MSI;
2.9. ensuring an efficient pricing mechanism for medicines;
2.10. ensuring a professional negotiation process of producer prices;
2.11. ensuring an effective functioning of the public procurement mechanism for MSI needs;
2.12. ensuring total transparency and excluding conflicts of interest in the public procurement process for medicines;
2.13. enlarging the list of covered prescription medicines;
2.14. developing incentive mechanisms to ensure the presence of generic drugs on the pharmaceutical market.

III. Ensuring a good quality of pharmaceutical services and a proper functioning of the pharmaceutical system

3.1. ensuring compliance of essential pharmaceutical services (corresponding to accreditation standards and standard operational procedures);
3.2. combating unfair competition in the pharmaceutical industry, preventing monopoly;
3.3. setting incentive rules for the implementation of advanced pharmaceutical services;
3.4. uninterrupted / timely information provision of the pharmaceutical act;
3.5. ensuring the observance of the legal requirements of the professionalism level of specialists in the pharmaceutical industry;
3.6. compliance with GPP requirements and Good Drug Distribution Practice (GDP) rules;
3.7. strengthening functional and efficient work of the pharmaceutical inspectorate;

3.8. regulating the principles of rational use of medicines;
3.9. streamlining the concept and procedures for accrediting pharmaceutical companies;
3.10. modifying the licensing process (authorization) of pharmaceutical activity and professional strengthening;
3.11. ensuring compliance with ethical marketing standards of medicines;
3.12. prevention of conflicts of interest and corruptibility in all the processes, procedures and functions of pharmaceutical activity;
3.13. strengthening safe procedures of harmless disposal of expired, discarded and damaged drugs;
3.14. compliance with professional requirements of pharmacist and assistant pharmacist;
3.15. strengthening the role of professional pharmacists' organizations in ensuring a good quality of pharmaceutical services and a proper functioning of the entire pharmaceutical system;
3.16. establishing and promoting the principle of "physician-pharmacist" collaboration for the benefit of the patient;
3.17. preventing and combating drug addiction and narcobusiness;
3.18. enhancing the development of dimensions of the clinical pharmacy concept.

The classification of factors that influence / characterize PhSS was carried out based on the results of scientific researches performed over some years at the "Vasile Procopisin" Social Pharmacy Department of *Nicolae Testemitan* SUMPh, at the National Institute of Pharmacy and the Medicines Agency [6, 9, 10, 13, 19, 20], as well as the rules and norms of medicine and pharmaceutical activity.

Based on the classification of factors, the analysis method was elaborated by applying the concept of quantitative - qualitative assessment by experts in the field of pharmaceutical safety. The analysis algorithm included: questionnaire elaboration; selecting experts; questioning process; analysis of questionnaire results; totalizations and conclusions.

Questionnaire elaboration. The purpose of the expert questionnaire was to carry out a multi-perspective assessment of the factors influencing / characterizing the pharmaceutical security system in the Republic of Moldova:

- duration of factors influence over time (short-term, medium-term, long-term and postponement);
- type of influence (positive, negative);
- influence dynamics (increasing, constant, decreasing);
- relative share of influence (very large, major, moderate, weak, insignificant);
- probability of factor action change (certainly will not change, may not change, 50% x 50%, possibly will change, will certainly change);
- quality of PhSS, taking into account the current state (during questioning) of the degree of safety provided by the pharmaceutical system in the Republic of Moldova (unsatisfactory, very low, low, medium, good, very good and excellent).

Selection of experts. The main criterion for selecting experts was "a broad professional vision" on pharmaceutical security issues. In order to evaluate the competence of future experts, face-to-face and telephone interviews [2] were applied. The criteria for selecting the experts were: workplace (Parliament of the Republic of Moldova, Government of the Republic of Moldova, Ministry of Health, Labor and Social Protection, AMMD, Pharmacy Faculty Administration of *Nicolae Testemitanu* SUMPh, SDC of *Nicolae Testemiţanu* SUMPh, PhARM, local drug producers, pharmaceutical warehouses, community and hospital pharmacies), work seniority, educational background, scientific title, authorship of scientific articles in the pharmaceutical field, a decision-making position in the pharmaceutical coordination system or in

state government departments. The quantification of the criteria allowed the preselected expert to accumulate min. 4.5 and max. 10 points.

In order to ensure a high level of competence of the selected experts, the minimum score limit of 7.5 was set.

In the selection process 23 specialists were enrolled; of them15 candidates passed the minimum score complying with all workplaces mentioned above.

To facilitate the calculation and subsequent analysis of questionnaire results, it was proposed to calculate the competence coefficient for each selected expert (Ke):

$$\text{Ke} = \frac{1}{10} \sum_{\text{P=7,5}}^{\text{P=10}} \text{Pa} \qquad (1)$$

where:

Pa - the number of points accumulated according to selected criteria.

Analysis of questionnaire results. The 15 experts (respondents), who met the selection criteria, were affiliated with the pharmaceutical system, the academic environment, organs of state power and other workplaces mentioned above.

Most respondents (experts) who passed the established minimum competence threshold (7.5 points) were teaching staff representatives of Pharmacy Faculty of *Nicolae Testemitanu* SUMPh, 4 in number. Two experts were selected from AMMD, community and hospital pharmacies, one expert represented another workplace.

Most experts (60.0%) have accumulated the competence coefficient equal to 0.9; 33,3% of experts - 0,8 and one expert (6,7%) – coefficient 7,5.

In order to highlight the prevalence of expert opinions, the "average number of experts" indicator ($\bar{M}$e) was applied that consistently mentioned the influence of factors, if the number of experts (Ne) was greater than or equal to $10 \geq 10$).

Assessment of factors ensuring / influencing efficacy, harmlessness and good quality of medicines.

In the chapter "duration of factors influence over time", the vast majority of experts mentioned "long-term". Thus, each factor included in this compartment was reported to be long-term on average by 14 experts $\bar{M}e = 14{,}00$).

The „type of influence" (positive or negative) was rated positive by all experts $\bar{M}e = 15{,}00$).

The dynamics of factors influence on PhSS has been predominantly mentioned as:

- stable – 7 factors ($\bar{M}e = 13{,}40$).
- increasing – 4 factors $\bar{M}e = 11.75$)

The analysis of the relative influence share of factors revealed a decreasing trend depending on the degree of influence. Therefore, the accumulated score of each factor (Pf) was determined according to the following formula:

$$\text{Pf} = \text{Ne} \times \text{PR}_n \qquad (2)$$

where: PRn – the relative share of factor (f = 1 ... 5).

The analysis results demonstrate the importance of undertaking constant measures to prevent the placement of falsified and substandard drugs (factor 1.10) on the pharmaceutical market. It is equally important to ensure the proper storage and transportation of medicines (rank 2 - factor 1.11), ensuring the quality of drug substances and excipients used in the production and preparation of drugs (rank 3-factor 1.4), but also compliance with GLP, GCP and GMP requirements (rank 4-factor 1.3).

Most experts have appreciated the likelihood of factor action change with the "not likely to change" rating ($\bar{M}e = 5,4$) and the „ertainly will not change" rating has averaged 1.93.

Assessment of factors ensuring / influencing physical and economic accessibility of drugs

Most factors in this group have long-term influence. This fact was mentioned by the majority of respondents-experts. "The type of factors influence" in this group as well as the first group was appreciated as positive $\bar{M}e = 1,00$ by all the experts.

The dynamics of factors influence was appreciated mainly by the respondents as follows: increasing – 10 factors ($\bar{M}e = 12,7$); stable – 4 factors ($\bar{M}e = 11,35$).

The „declining" rating was assigned to 3 factors by only 6 experts ($\bar{M}e = 2,00$).

Of the 14 factors influencing the accessibility of medicines, "ensuring the presence of essential drugs, including the covered prescription medicines" was ranked first according to "relative share". The second important factor is "the existence of an efficient mechanism of price formation for medicines" (factor 2.9). The "uniform demographic and geographic distribution of community pharmacies throughout the country" was ranked third.

The importance of a legal norm on the minimum mandatory range of medicines in community pharmacies and pharmaceutical warehouses (rank 4) has been highlighted.

Assessment of factors ensuring / influencing a good quality of pharmaceutical services and a good functioning of the pharmaceutical system.

Like the factors in the two groups set out above, the factors of this group predominantly manifest long-term action. Of 18 factors, a long-term action has been unanimously assessed by all experts ($\bar{M}e = 15$) in 6 factors.

Also, the experts unanimously assigned a positive influence of factors – $\bar{M}e = 15$ to this group of factors.

The respondents assessed the "dynamics of factors influence" in this group as follows:

- increasing - 8 factors (3.1, 3.2, 3.5, 3.5, 3.8, 3.12, 3.15 and 3.17), ($\bar{M}e = 10,75$);
- the "decreasing" rating was attributed mainly to a single factor – 3.9 ($\bar{M}e = 11,00$);
- stable dynamics of influence was predominantly assessed in the remaining 9 factors ($\bar{M}e = 11,55$).

The assessment results of the relative share of factors in this group on PhSS demonstrate that the experts predominantly appreciated 11 factors ($\bar{M}e = 11,91$). In this group, the primacy belongs to factor 3.6: "compliance with the requirements of GPP Good Distribution Practice for Medicines/Pharmaceutical Products (GDP)"- rank 1 with the maximum number of accumulated points – 75. Rank 2 is "strengthening the role of professional pharmacists' organizations in ensuring a good quality of pharmaceutical services and a good functioning of the whole Pharmaceutical system". Rank 3 was assigned to factor "compliance with professional requirements of pharmacist and assistant pharmacist", 73 points being accumulated.

The probability of factors action change was assessed by the respondent experts as follows:

- „definitely will change" – 4 factors (3.1.3.6.3.9 and 3.10) – refer mainly to value $\bar{M}e = 12,00$;
- „will possibly change" (3.2 and 3.4) – $\bar{M}e = 10,00$;
- „may or may not change" (50% x 50%) – 4 factors (3.8, 3.12, 3.13 and 3.15), $\bar{M}e = 10,75$;
- „may not change" – 13 factors with $\bar{M}e = 2,46$;
- „certainly will not change" – 5 factors with $\bar{M}e = 2,00$.

The factors action change on PhSS needs to be monitored and coordinated to ensure effective management of PhSS.

As a result of the analysis, the average scores of a factor were determined. This allowed

appreciating the importance of the three groups of factors influencing PhSS and the order of priorities to consider in PhSS development and consolidation.

Thus, the group of factors influencing the provision of physical and economic accessibility of medicines with the average score of 65.57 was ranked first; the second place was assigned to group no. I - with an average score of 59.09 and the third place with 55.28 points - group no. III of factors.

Assessment of the quality of pharmaceutical security system

Assessing the quality of any system is a complex problem resulting from the multitude of component elements, processes, functions, determinants and additional influence. In view of this fact and considering that PhSS is in the process of argumentation and elaboration, we intend to apply as a concept of quality assessment of PhSS - the quality corresponding to the final purpose of the system. In order to accomplish this intermediate task of the research, the method of questioning the experts was used. In questionnaire no.1, the last referral-proposal to the experts was assigned to PhSS quality: "Quality assessment of the pharmaceutical security system (QS), taking into account the current state of safety provided by the pharmaceutical system" of the Republic of Moldova. In order to assess the quality of this system, it was proposed to apply the scale of 7 points: -3 (unsatisfactory quality); -2 (very low quality); -1 (low quality); 0 - (average score ± 0.5); +1 (good quality) +2 (very good quality); +3 (excellent quality). To perform the final quantification of each expert's opinion, it was proposed to determine the relative quality factor (Kc), which is the product of the 7-point rating and the competence of the expert:

$$Kc_i = Ae_i \times Ce_i, \quad (3)$$

in which: Ae_i - the PhSS quality assessment given by expert i;

Ce_i – the degree of expert i competence.

Following the expertise, two experts appreciated the quality of PhSS as "good" (+1 point); two other experts considered it "average" (± 0.5 points); 3 - "low" (-1 point), 2 rated it "very low" (-2 points) and 2 experts - "unsatisfactory" (-3 points).

To determine the average value of PhSSF quality factor, the average k_c was determined:

$$\overline{Kc} = \sum_{i=1}^{i=N} Kci/Ne, \quad (4)$$

in which: Ne - the number of experts-respondents.

Considering the application of the 7-point scale, it was necessary to develop the final quality assurance scheme of PhSS presented in Table 2.

Table 2. **Assessment of the quality of pharmaceutical security system**

PhSS Quality Rating	Interval of $\overline{Kc}$coefficient
Excellent	≥ + 2,5 …….+ 3,0
Very good	≥ + 1,5 …….+ 2,4
Good	≥ + 0,5 …….+ 1,4
Medium	± 0,01 …….± 0,09
Low	≤ - 1,0……. - 1,5
Very low	≤ - 1,6 ……. – 2,6
Unsatisfactory	≤ - 2,7 ……. -3,0

The result of calculating $\overline{Kc}$ value, equal to - 1.03, denotes that experts consider the quality of the pharmaceutical security system to be "low". This appreciation is in line with the analysis results of factors influencing the pharmaceutical security in the Republic of Moldova.

3. ENSURING PHARMACEUTICAL SECURITY LEGISLATION

The analysis of the legislative and regulatory framework in medicine and pharmacy, health, security and other areas that could regulate the pharmaceutical security allowed us to highlight the absence of legal norms, which would directly address the pharmaceutical security issues. The phrase "pharmaceutical security " is not found in any legal norm of the legislation of the Republic of Moldova. This fact suggests another interim conclusion: legal norms intended to ensure the pharmaceutical security in the Republic of Moldova are indirect rules, namely rules that establish requirements, criteria, powers, definitions, etc., aimed at ensuring pharmaceutical security safety.

The notion of pharmaceutical security is not found in the Regulations of organization and operation of:

- The Ministry of Health, Labour and Social Protection, approved by Government Decision no. 694 of 30.08.2017;
- The Agency of Medicines and Medical Devices, approved by Government Decision no. 71 of 23.01.2013 – the two public bodies responsible for the implementation of the state health policy as well as medicines and pharmaceutical policy, respectively. [1]*

Determining the legal coverage of pharmaceutical security.

Since 2015, recommendations and notions on some safety issues of pharmaceuticals have appeared in various reports, speeches and decisions of public authorities [7, 16].

This part of research is aimed at detecting some legislative gaps in the field of pharmaceutical security.

Initially, all normative-legislative acts regulating the pharmaceutical security were selected. Legislative-normative acts have been systematized according to two principles:

I – field of legislation: medical, pharmaceutical and others;

II – subsystems of pharmaceutical security system [7].

Overall the legislative and normative acts containing norms meant to ensure the pharmaceutical security comprise 112 acts, including pharmaceuticals - 78, medical - 26, other domains - 8.

Analysis method

An algorithm [4] was ***developed***, which was used as a methodical tool to establish the degree of legislative-normative coverage of pharmaceutical security.

Stage I. *De facto analysis of the pharmaceutical system background.*

All the conditions necessary to ensure pharmaceutical safety were marked by Cn. The number of necessary conditions can be determined as the general number of Cn conditions or the totality of conditions of providing pharmaceutical safety:

Ccm - conditions for ensuring quality, efficacy and harmlessness of medicines;

Cam - conditions for ensuring accessibility (physical and economic) of medicines;

Cca - conditions for ensuring quality of the pharmaceutical act (pharmaceutical services and good functioning of the entire pharmaceutical system).

Stage II. *Highlighting the existence / absence of legal norms legalizing the application of various ways, methods, processes, procedures, norms and other measures that would impose*

* The author of the thesis considers that in these two regulations the attribution for ensuring pharmaceutical safety and the responsibility for ensuring it should not be omitted.

compliance with the necessary conditions for ensuring the pharmaceutical security.

This stage was carried out with the application of the expertise method combined with the participatory consultation technique Delphi [17]. Experts have been enrolled to meet the requirements in section 2.

Each of the 15 selected experts was offered a questionnaire to assess the compliance with the conditions of the pharmaceutical safety legislation (as set out in Questionnaire 2) and how to assess the legal coverage [7]: the existence of the necessary legal norm - 1 point; absence of legal norm – 0 points; if there is the necessary legal norm, non-compliance with legal norm – 0,5 points; the regulation designed to ensure pharmaceutical security is ineffective – 0,5 points.

Legislative coverage of the conditions for ensuring pharmaceutical security has been marked by Ne - existing legal norms meant to ensure the observance of the necessary conditions to ensure the pharmaceutical security.

The Ne indicator as well as Ca was highlighted for the total number of existing rules or directions to ensure pharmaceutical security:

Necm – *de facto* legal rules covering the conditions of ensuring pharmaceutical security by ensuring quality, efficacy and harmlessness of medicines;

Neam – *de facto* legal norms that ensure physical and economic accessibility of medicines;

Neca – *de facto* legal norms that ensure quality of the pharmaceutical act.

Stage III. *Determining the degree of legislative coverage of the requirements for ensuring pharmaceutical security.*

This indicator was marked by ALn - for the total number of existing legal norms and conditions, and for the three directions of pharmaceutical security, respectively

$$\text{ALcm} = \frac{\text{Necm}}{\text{Ccm}} \quad (5)$$

where: ALC – is an indicator of legal coverage of the pharmaceutical security by ensuring quality, efficacy and harmlessness of drugs;

$$\text{ALam} = \frac{\text{Neam}}{\text{Cam}} \quad (6)$$

where: ALam – is an indicator of legal coverage of the pharmaceutical security by ensuring physical and economic accessibility of medicines;

$$\text{ALca} = \frac{\text{Neca}}{\text{Cca}} \quad (7)$$

where: ALca – is an indicator of legal coverage of the pharmaceutical security by ensuring quality of the pharmaceutical act and good functioning of the entire pharmaceutical system.

Stage IV. *Elaboration of the quantification scale of the degree of legislative coverage of the pharmaceutical security.*

Since the value of the Aln indicator can vary between "zero" and "one", a clearly defined rating scale has been developed.

For a clearer perception of the ALn indicator, its value was multiplied to 10. Thus, the amplitude of the indicator varied between 1 and 10. For quantification, the following scale of assessment was proposed: ALn = 0-null; ALn => 0 ... 2 - vulnerable; ALn => 2 ... 5 - insufficient; ALn => 5 ... 8 - moderate; ALn => 8 ... <10 - good; ALn = 10 - total.

Thus, the final formula for calculating the degree of legislative coverage of ensuring pharmaceutical security (LCn) is as follows:

$$\text{ALn} = \frac{\text{Ne}}{\text{Cn}} \text{ x } 10 \quad (8)$$

where: Ne - the number of existing legal norms intended to ensure pharmaceutical security;

Cn – the number of conditions required to ensure pharmaceutical security.

Each of the 15 experts enrolled in the questionnaire expressed his/her opinion, assessing the existence / absence of the respective legal norm and / or the existing but non-compliance or inefficiency of the existing norm. The views of all experts coincided in 39 conditions (90.7%). In four pharmaceutical safety regulatory conditions (1.5, 2.12, 3.8 and 3.9), the opinions of 3 experts (20%) were different. Applying the participatory method of expert consultation (Delphi method), a consensus has been reached and the results of the evaluation have coincided with the whole group of experts.

Summing up the data of the experts' estimation, the degree of legislative coverage of the necessary conditions for ensuring the pharmaceutical security in the Republic of Moldova was calculated (table 3).

Table 3**. Legislative coverage of the pharmaceutical security in the Republic of Moldova**

Domain	Legislative coverage				Degree of coverage
	Existence of rules	Absence of norms	„non-compliance", "insufficiency"	Accumulated points	
1. Ensuring efficacy, harmlessness and good quality of medicines	6	3	2	7	6,36 Moderate
2. Ensuring physical and economic accessibility of medicines	-	7	7	3,5	2,50 Insufficient
3. Ensuring good quality of pharmaceutical services and proper functioning of the pharmaceutical system	1	10	6	4	2,22 Insufficient
The whole pharmaceutical security system	7	20	15	14,5	3,37 Insufficient

The data in Table 3 show that the legislative coverage of pharmaceutical security in the Republic of Moldova is insufficient. All areas require completion or development of new legal norms, but some issues like good quality of pharmaceutical services and good functioning of the pharmaceutical system as well as ensuring accessibility of medicines are poorly regulated. The obtained results are indicative of legislative gaps affecting the pharmaceutical security and can serve as reference points for the legislative activity in the pharmaceutical field.

Highlighting and quantifying risk factors

Definition: "Risk is the problem (situation, event, etc.) that has not yet occurred, but which may occur in the future; any risk can threaten or impede the obtaining of the previously fixed results" [15]. Taking into account this definition, the classification of risk factors in the pharmaceutical security system was developed (Table 4).

In order to ensure the accuracy of the developed classification as well as to quantify the risk factors, the questioning of the experts was carried out, applying the methodological arsenal presented in the compartment 2 of the summary.

Based on the classification of risk factors presented in Table 4, a questionnaire was worked out. As a result of the questionnaire the following points were made:

- the list of 14 risk factors proposed for analysis was unanimously accepted by all experts;
- only 2 factors (1.1 and 3.5) were assessed as insignificant by two experts - each factor - by an expert;
- the experts have not proposed any additional risk factors.

The results of the assessment performed by experts showed that most of the factors (8 out of 14 - 57.14%) were rated 5 (risk with very high influence: critical, threatening) by at least 10 experts out of 15 (66.7%).

Table 4. **Classification of risk factors in the pharmaceutical security system**

Group	Factors
I. Ensuring efficacy, harmlessness and good quality of medicines	1.1. Breaching the norms on the proper functioning of the marketing authorization process for medicines. 1.2. Presence on the pharmaceutical market of medicines not controlled or controlled but of poor quality. 1.3. Breaching the norms on drug storage.
II. Ensuring physical and economic accessibility of medicines.	2.1. Absence (disappearance) of medicines required by the health system in the pharmaceutical market. 2.2. Absence of state reserves of drugs necessary for exceptional situations. 2.3. Unjustified price increase for medicines. 2.4. Low level of purchasing power of the population.
III. Ensuring good quality of pharmaceutical services and proper functioning of the pharmaceutical system.	3.1 Illicit import of drugs, including counterfeits. 3.2 Corruptability of Centralized Medicines Public Procurement. 3.3 Transforming ethical pharmacy into a commercial pharmacy. 3.4 Involving non-specialists in pharmaceutical activity. 3.5 Absence of a sustainable mechanism for harmless destruction of drugs 3.6 Abusive and inappropriate advertising of drugs. 3.7 Decreasing the role of control function on pharmaceutical activity.

The obtained results demonstrate the following:

- the 2nd group is the most important group of risk factors (ensuring physical and economic accessibility of medicines), being characterized by the average value of accumulated points for a factor equal to 67,75. Each expert rated this group of factors averaging 4.52 points. The most important factor in this group is 2.2 - the absence of state reserves of medicines needed for exceptional situations;
- the 3rd group of factors (ensuring good quality of pharmaceutical services and good functioning of the pharmaceutical system) was ranked second, with an average value of accumulated points of 65.14 for a factor. On average, each factor in this group obtained 4.34 points from each expert. The most important factor in this group is 3.3 - the transformation of ethical pharmacy into a commercial pharmacy;
- the 1st group of factors was ranked third (ensuring effectiveness, harmlessness and good quality of medicines), the average value of accumulated points being equal to 60.00 and the average amount accumulated by each factor being equal to 4.00. The most important factor in this group is 1.2 - the presence on the pharmaceutical market (possible presence) of medicines not subject to quality control or being quality non-compliant;
- of the entire list of risk factors, factor 2.2 is ranked first with 75 accumulated points, factor 3.3 is ranked second with 74 accumulated points, and factor 1.2 is ranked third with 72 accumulated points. The range of risk factors is followed by factors 3.1 (illicit drug import); 2.1 (absence of necessary drugs); 2.3 (unjustified price increase for medicines); 3.2 (corruptibility of public procurement) etc.

The results of the studies conducted and presented in chapters 2 and 3 of the research paper served as arguments for the elaboration of recommendations submitted for implementation.

Strengthening the legal ensuring of pharmaceutical security could be achieved in two ways: a) developing, promoting and adopting a new law on pharmaceutical security; b) modifying and completing the existing legislative framework.

Considering the interdependence of PhSS with other health systems / subsystems, as well as state security, a series of recommendations were made in order to make amendments and additions to the existing legislative framework.

4. PHARMACEUTICAL SECURITY MANAGEMENT

In 2003, according to the Government Decision [28], an interparliamentary control commission was set up to ensure the security of pharmaceutical assistance and counteract the illicit import of medicines; the regulation of the Commission has been approved and the purpose has been established "Supervising and monitoring the work of services responsible for ensuring import, production, distribution and marketing of medicines and improving the level of monitoring of the pharmaceutical market". The Government Decision was in force until 10 February 2014, when it was repealed by Decision no. 96 [29]. The activity of the Commission was a first attempt to build a pharmaceutical security system in the Republic of Moldova, but it failed.

From the methodological point of view, the pharmaceutical security management is based on 4 pillars that underpin the managerial systems: theoretical, methodical, legislative and organizational ones.

The theoretical basis of the pharmaceutical security system has been addressed in Chapter II of the thesis; the legal basis in Chapter III, the methodical basis has been applied in the whole thesis contents, the organizational basis is exposed in Chapter IV.

The key role in ensuring the functioning of the pharmaceutical security system lies in the staff involved, which makes the need for continuing training of the staff in the field of pharmaceutical security.

The need to create and strengthen the pharmaceutical security system calls for active involvement of professional pharmacists' organization, which, based on professional approaches, is a clear decision-making power, especially aimed at excluding non-specialist involvement in pharmaceutical activity.

Informing society about the role of pharmaceutical security and the real situation in this regard has a dual importance: on the one hand, citizens need to know their rights and responsibilities; on the other hand, an informed society can make the decision makers accountable for ensuring the pharmaceutical security.

Based on the theoretical postulates and practical situation in the Republic of Moldova, the general scheme of the pharmaceutical security system functioning was developed (Figure 1).

The good functioning of the coordination, regulation and control subsystem, to a certain degree, depends on ensuring its functionality on hierarchical levels.

The current particularities of the pharmaceutical system hierarchy in the Republic of Moldova are conditioned to a great extent by the liquidation of the district coordination level, which has been carried out in two stages since the last decade of the last century:

phase I - starting with disorganizing district pharmacies;

phase II - liquidation of the position of interdistrict pharmacist – inspector.

Thus, the process of ensuring the pharmaceutical security of RM can be influenced at 3 levels: „zero” or national; „one” or organizational; „two” or professional.

At zero level, the main means of influence is regulation and control, while at the other two levels this means is reduced to implementing policies, executing decisions, and, of course, demonstrating the professional skills of specialists in the field. At the same time, one has to take into account the internal character of the possibilities of influence over pharmaceutical security system: the three subsystems of PhSS can be influenced at all of three hierarchical levels. Only the degree of influence varies from level to level. To rank the degree of influence, it was arbitrarily considered conventional: A – great influence; B – medium influence; C – small influence.

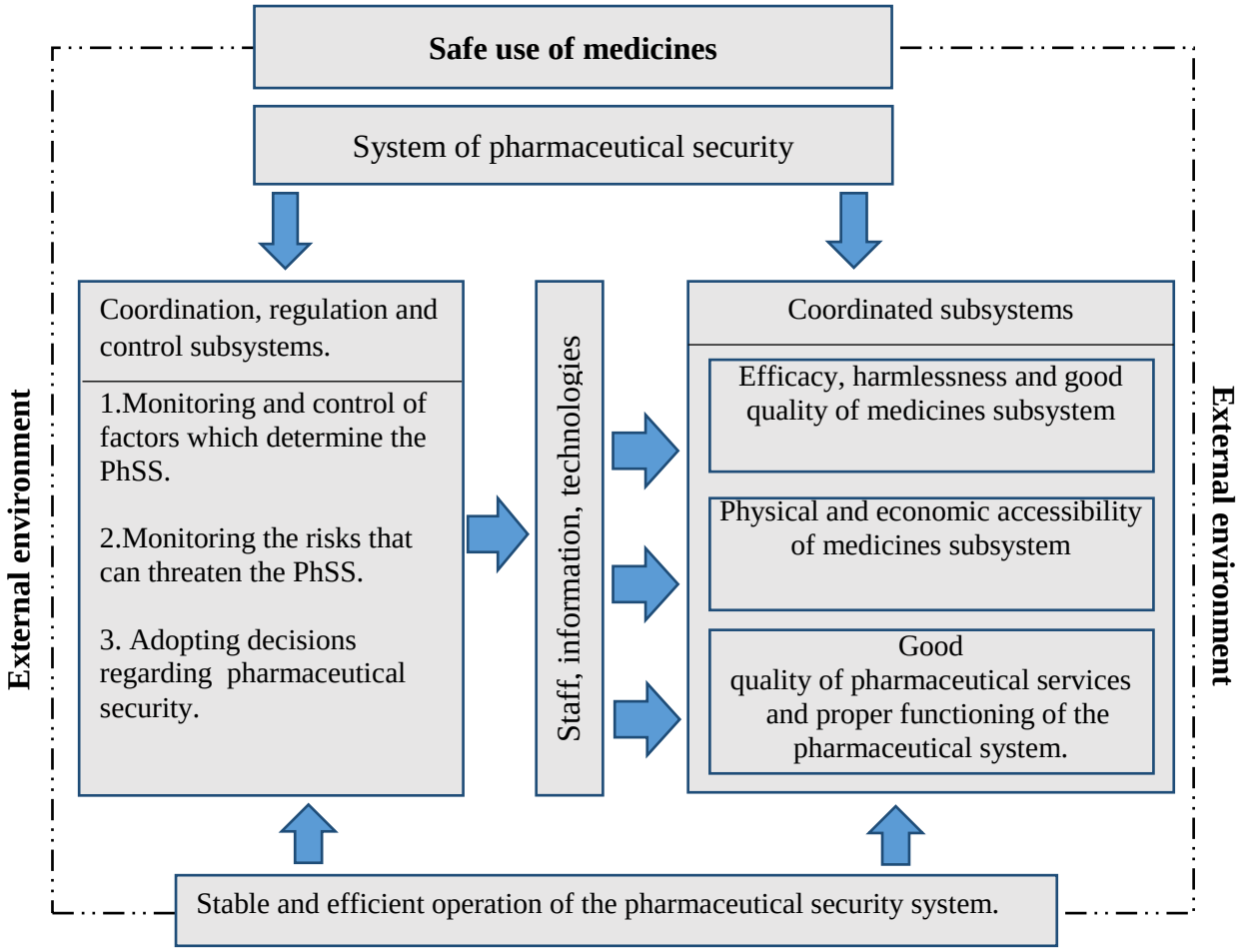

Figure 1. **Functionality of the pharmaceutical security system.**

This convention allowed the development of the decision matrix on ensuring the functionality of the pharmaceutical security system (Table 5).

In order to render the decision matrix (Table 5) the importance of practical applicability, the functions and conditions for ensuring the pharmaceutical security have to be implemented, as well as their distribution on hierarchical levels: national, organizational and professional.

Table 5. **The decision matrix on ensuring the functionality of PhSS**

Hierarchical levels / **Subsystems of pharmaceutical security**	**Level Zero (national), Coordination and control**	**Level One (organizational)**	**Level Two (professional)**
Ensuring efficacy, harmlessness and quality of medicines.	**A**	**B**	**C**
Ensuring accessibility of medicines	**B**	**A**	**C**
Ensuring quality of pharmaceutical services and operation of the pharmaceutical system	**C**	**B**	**A**

The conventionality of the degree of influence indicated in Table 5 and materialized by the distribution of functions and conditions on hierarchical levels consists in the fact that the decisions regarding pharmaceutical security ensuring, adopted at different hierarchical levels, are not strictly limited by levels: some decisions can be adopted only at one level (ex: adoption of legislative and normative acts) and others at 2-3 levels (ex: implementation and observance of professional requirements and norms, real contribution to the prevention and fight against drug addiction and narco-business, etc.).

CONCLUSIONS

1. The following definition of pharmaceutical security has been established: creating a situation where any danger or threat arising from the pharmaceutical system or pharmaceutical activity for the public health and for every human being is excluded.
2. The specific actions aimed at ensuring the pharmaceutical security at different levels were highlighted:
   - worldwide: preventing / combating counterfeit and falsified drugs and medicines theft in the process of traceability;
   - regional: serialization, search for alternatives to patenting innovative medicines, exclusion of conflicts of interest in the process of medicines circulation;
   - national: obtaining benefits for the health of medicine consumers, import independence, accessibility for consumers.
3. The multicomponent, systemic nature of pharmaceutical security was demonstrated and the main components and factors of influence were highlighted:
   - effectivness, harmlessness and good quality of medicines;
   - physical and economic accessibility of medicines;
   - good quality of pharmaceutical services and proper functioning of the entire pharmaceutical system.
4. A complex method of analyzing the influence of all the factors on the pharmaceutical security has been elaborated which includes estimation of influence duration, the type, the dynamics, the relative share of influence and the probability of change of different factors.
5. The most important influence on the national pharmaceutical security system has been pointed out: factors determining the physical and economic accessibility of medicines; factors ensuring quality, efficiency and harmlessness of medicines have been ranked second; the last place belongs to the group of factors ensuring a good quality of pharmaceutical services and a good functioning of the entire pharmaceutical system.
6. The real situation regarding the quality of pharmaceutical security in the Republic of Moldova has been estimated; it ranged within +3..- 3 scale, proving to be "low" (kc = -1.03).
7. It has been demonstrated that in the Republic of Moldova the pharmaceutical security is regulated only by indirect legal norms and, most of them (77.8%) do not provide any sanctions which are a constitutive element of the legal norm.
8. The insufficient degree of legislative coverage of the national pharmaceutical security was demonstrated: within the range of 0 ... 10, the legal coverage coefficient represents an average of 3.37 - "insufficient", including:
   - ensuring efficacy, harmlessness and good quality of medicines, the ALn coefficient = 6.36, which is "moderate";
   - ensuring physical and economic accessibility of medicines, ALin = 2.50 - "insufficient";
   - ensuring a good quality of pharmaceutical services and a good functioning of the pharmaceutical system, ALn = 2,22 - "insufficient".
9. The risk factors for ensuring national pharmaceutical security were highlighted as follows:
   - absence of state reserves of medicines required for exceptional situations (75 accumulated points);
   - transformation of the ethical pharmacy into a commercial pharmacy (74 accumulated points);
   - presence on the pharmaceutical market of medicines which are not subject of quality

control or medicines, subject to control but being of non-conforming quality (72 accumulated points).

10. The functionality framework of the pharmaceutical security system has been established and demonstrated, including the functions and conditions for ensuring the security at three hierarchical levels in the Republic of Moldova: national, organizational and professional, was argued and elaborated. Recommendations were made to strengthen the national pharmaceutical security management.

REFERENCES

1. Bale H. *Contrafacerea produselor farmaceutice: probleme, tendințe, măsuri. Atelier OMPI/OECD*. Disponibil la: www.oecd.org/sti/ind/35650404.pdf [accesat la 28.04.2017].
2. Brătucu G., Brătucu T.-O. *Metode calitative utilizate în cercetarea pieței*. Disponibil la: www.managementmarketing.ro/pdf/articole/4.pdf [accesat la 29.05.2018].
3. Bruls H., Wyer D. *Pharmaceutical cargo theft in Europe. A realistic view of the current trends, challenges, and financial impacts*. Disponibil la: https://files.carrier.com/sensitech/en/contentimages/FWIEuropeanPharmaweb.pdf [accesat la 29.04.2017].
4. **Buliga V.** Analysis of the legislation of the Republic of Moldova în terms of pharmaceutical security. *The Moldovan Medical Journal.* 2017; 60(1): 10-14. ISSN: 2573-6373.
5. **Buliga V.** Puncte de reper conceptuale privind tehnologia cercetării securității farmaceutice. În: Materialele conferinței științifice cu participare internațională. „De la design-ul medicamentului la calitate și inofensivitate", în memoria prof. Filip Babilev „80 ani de la naștere". *Revista farmaceutică a Moldovei,* 2016; 1-4: 29. ISSN: 1812-5077.
6. **Buliga V.**, Safta V. Accesibilitatea medicamentelor – indicator al nivelului de asistență farmaceutică. *Buletinul INF*, 2002; 12: 14-17.
7. **Buliga V.**, Safta V., Adauji St., Luța A. Repere conceptuale privind securitatea farmaceutică. *Moldovan Journal of Health Sciences*, 2016, 7 (1), 78-87. ISSN: 2345-1467.
8. **Buliga V.**, Safta V. Principiile abordării sistemice și aplicarea lor în domeniul farmaceutic. În: *Materialele conferinței științifice cu participare internațională „Farmacia etică: istorie, realități și perspective",* Chișinău; 19-21.04.2018, p.53-57. ISBN 978-9975-3159-5-1.
9. **Buliga V.** Studii privind perfecționarea mecanismului de procurare a medicamentelor din bani publici. În: *Materialele conferinței științifice anuale „Ziua medicamentului la INF. De la idee la farmacie",* Chișinău; 2003, p. 264-279. ISBN 9975-78-291-4.
10. **Buliga V.** Unele caracteristici ale sistemului distribuirii angrosiste a medicamentelor în Republica Moldova. În: *Materialele conferinței științifice anuale „Ziua medicamentului la INF. De la idee la farmacie",* Chișinău; 2004, p. 19-23. ISBN 9975-9811-0-0.
11. Conceptul de securitate. Sectorul de securitate. Institutul de Politici Publice. Rezumat informativ pentru jurnaliști. Disponibil la: http://www.ipp.md/old/public/files/Proiecte/1-conceptul_securitate.pdf [accesat la 02.02.2016].
12. În Iași, Brașov și Cluj-Napoca au apărut panouri care îndeamnă oamenii să se informeze despre vaccinuri. Departamentul Zamolxe România, 2017. Disponibil la: https://www.dzr.org.ro/iniase-…-vaccinuri… [accesat la 02.01.2018].
13. Lupu M., **Buliga V.,** Safta V., Buzu A. Evoluția prețurilor pentru medicamente în Republica Moldova. În: *Culegerea „Al. VI-lea Congres al farmaciștilor din Republica Moldova,* Chișinău, 2009, p. 23-24.
14. Maurg Pasquier L. Sănătatea publică și interesele industriei farmaceutice: cum să garantăm

primatul intereselor sănătății publice. Raport. *Asambleea Parlamentară a CE*. 2015, Doc. 13869.

15. Metodologie de implementare a standardului de control intern „Managementul riscurilor". Ministerul Finanțelor Publice al României, 2007. Disponibil la: https://cis01.central.ucv.ro/manag_ac_ad/2011/files/metodologie_risc.pdf [accesat la 20.07.2018].
16. Pharmaceutical Security organizations: reducing risk on a global scale. Disponibil la: https://www.pharmoutsourcing.com/Featured-Articles/178381-Pharmaceutical-Security-Organizations-Reducing-Risk-on-a-Global-Scale/ [accesat la 28.04.2017].
17. Pasaniuc, J-D. *Metoda Delphi – metoda participativă de consultare a experților*. Disponibil la: www.facilitare.ro/ghidul-complet-al-facilitării/2009/11/02/metoda-delphi [accesat la 08.06.2017].
18. Roberts R.I. *Un secret teribil al industriei farmaceutice: medicamentele nu sunt elaborate ca să vindece bolile. Jurnal Paranormal. 2016*. Disponibil la: https://jurnalparanormal.ro/contrent/un-secret-%E2%80%A6-vindece/. [accesat la 02.01.18].
19. Safta V., Brumărel M. Calitatea actului farmaceutic şi accesibilitatea medicamentelor, *Revista farmaceutică a Moldovei*. 2014; 1-2: 21-23. ISSN: 1812-5077.
20. Safta V., **Buliga V.,** Chiţan E., Lupu M. Căi de fortificare a asigurării cu medicamente în Republica Moldova. *Akademos. Ştiinţe medicale.* 2016; 1: 77-85. ISSN: 1857-0461.
21. Safta V. Repere analitice privind aplicarea principiului „Scopului final" al abordării sistemice în practica farmaceutică. *Revista farmaceutică a Moldovei*. 2014; 3-4: 20. ISSN: 1812-5077.
22. Walter E., Dragosits A., Said M. Access to pharmaceutical products în six European countries – analysis of different pharmaceutical distribution systems. Farmaeconomia. *Health economics and therapeutic pathways*. 2012, 13(1), 33-41. Disponibil la https://journals.seedmedicalpublishers.com/index.php/FE/article/view/192/188 [accesat la 08.06.2017].
23. Аносов И.С. Формирование системы взаимодействия субъектов обращения лекарственных средств на основе концепции фармацевтической безопасности. Автореферат диссертации кандидата фармацевтических наук. М. 2016, 24 стр.
24. Пархоменко Д.В. Теоретические основы организационно-методические подходы к обеспечению национальной безопасности РФ в сфере обращения лекарственных средств. Автореферат диссертации доктора фармацевтических наук М 2005, 48 с.
25. Системный подход. Гуманитарная энциклопедия. Аналитический портал ISSN 2310-1792. Disponibil la: https://gtmarket.ru/concepts/7095 [accesat la 27.01.2018].
26. Системный подход. Словари АКАДЕМИК. Disponibil la: https://dic.academic.ru/dic.nsf/ruwiki/118429 [acccesat 27.01.2018].
27. Hotărîrea Guvernului RM nr.1222 din 10.10.2003 despre instituirea Comisiei interdepartamentale de control pentru asigurarea securității asistenței farmaceutice și contracararea importului ilicit de medicamente. MOF nr. 218-220 din 24.10.2003, art. nr. 1276.
28. Hotărîrea Guvernului nr. 96 din 10.02.2014 cu privire la abrogarea unor hotărâri ale Guvernului. MOF nr. 35-41 din 2014, nr. 113.

LIST OF PUBLICATIONS ON THE THESIS THEME

1. Сафта В., **Булига В.** Реформа системы фармацевтического координирования в Республике Молдова. Seminarul „Лексети” și reuniunea IV-a a AFRM „Direcții prioritare ale activității farmaceutice în condiții de reformă a sistemului de sănătate”. Buletinul INF, 1999, nr. 6, p. 13.
2. Safta V., **Buliga V**., Lupu M., Popa A. Analiza importului de produse farmaceutice în Republica Moldova. În: Rezumatele lucrărilor științifice ”Farmacia Moldovei – realizări și perspective. Conferință științifică consacrată jubileului de 35 ani de la fondarea facultății Farmacie”, Chișinău, CEP Medicină al USMF, 1999, p. 27.
3. Сафта В.Н., Лупу М. Н., **Булига В.Г.** О формировании сортимента лекарств для оказания бесплатной медицинской помощи гарантированным государством. В: VII Российский национальный конгресс „Человек и лекарство”, М, 2001, с. 672.
4. Stratu V., Bulmaga A., Safta V., **Buliga V.** Efecte economico-sociale în activitatea secțiilor extrabugetare ale farmaciilor bugetare de spital. În: Materialele I-ei conferințe științifice cu participare internațională a specialiștilor din economie, finanțe și organizare a activității instituțiilor medicale din Republica Moldova „Aspecte economice și financiare în reforma sistemului de sănătate”, Chișinău, 2002, pag.150-153.
5. **Buliga V**., Safta V. Accesibilitatea medicamentelor – indicator al nivelului de asistență farmaceutică. Buletinul INF, 2002, nr.12, pag.14-17.
6. **Buliga V.** Studii privind perfecționarea mecanismului de procurare a medicamentelor din bani publici. În: Materialele Conferinței științifice anuale „Ziua medicamentului la INF” cu tema „Medicamentul de la idee la farmacie”, Chișinău, 2003, pag. 264-279. ISBN 9975-78-291-4.
7. Brumărel M., Safta V., **Buliga V**., Pașa O. Elaborarea sistemului computerizat de prelucrare a informației la INF. În culegerea: Materialele Conferinței științifice anuale „Ziua medicamentului la INF” cu tema „Medicamentul de la idee la farmacie”, Chișinău, 2003, p. 351-358. ISBN 9975-78-291-4.
8. **Buliga V.** Unele caracteristici ale sistemului distribuirii angrosiste a medicamentelor în Republica Moldova. În culegerea: Materialele conferinței științifico-practice „Ziua medicamentului la INF. Medicamentul de la idee la farmacie”, Chișinău, 2004, p.19-23. ISBN 9975-9811-0-0.
9. Lupu M., **Buliga V**., Safta., Buzu A. Evoluția prețurilor pentru medicamente în Republica Moldova. În culegerea „Al VI-lea Congres al farmaciștilor din Republica Moldova, Chișinău, 2009, p. 23-24.
10. Safta V., **Buliga V.,** Chiţan E., Lupu M. Căi de fortificare a asigurării cu medicamente în Republica Moldova. *Akademos. Ştiinţe medicale.* 2016; 1: 77-85. ISSN: 1857-0461
11. **Buliga V.** Puncte de reper conceptuale privind tehnologia cercetării securității farmaceutice. În: Materiale conferinței științifice cu participare internațională. ”De la design-ul medicamentului la calitate și inofensivitate”, în memoria prof. Filip Babilev” 80 ani de la naștere. Revista farmaceutică a Moldovei, 2016, nr. 1-4, p. 29. ISSN 1812-5077.
12. Сафта. В. Н., Брумэрел М. Д., Адаужи С. Б., **Булига В. Г.,** Багу А. Социальные аптеки и их роль в системе здравоохранения. В: Соціальна Фармація в охороні здоров’я. Харків. 2016, 2(4), с. 11-17, ISSN: 2413-6085.
13. **Buliga V.,** Safta V., Adauji S., Luța A. Repere conceptuale privind securitatea farmaceutică. Moldovan Journal of Health Sciences, 2016, 7 (1), 78-87. ISSN 2345-1467.
14. **Buliga V.** Analysis of the legislation of the Republic of Moldova in terms of pharmaceutical security. The Moldovan Medical Journal, 2017, (1), 10-14. ISSN 2537-6373.
15. Adauji S., **Buliga V.,** Safta V., Brumărel M., Lupu M., Spinei L. Argumentation of the strategic directions for the development of pharmaceutical system in the Republic of Moldova. The Moldovan Medical Journal, 2017, (1), 26-31. ISSN 2537-6373.
16. **Buliga V.,** Safta V. Principiile abordării sistemice și aplicarea lor în domeniul farmaceutic. În: Materialele conferinței științifice cu participare internațională „Farmacia etică: istorie, realități și perspective”, Chișinău, 2018, p. 57-61. ISBN 978-9975-3159-5-1.