UDC 615.015.32:615.11:006.44(477)+(4)
DOI https://doi.org/10.32689/2663-0672-2024-1-19

Liliia VYSHNEVSKA
Doctor of Pharmaceutical Science, Professor, Head at the Department of Drug Technology, National University of Pharmacy, liliiavyshnevska@gmail.com
ORCID: 0000-0002-6887-3591

Svitlana OLIINYK
Candidate of Pharmaceutical Sciences, Associate Professor at the Department of Drug Technology, National University of Pharmacy, sveta_oleinik@ukr.net
ORCID: 0000-0002-6638-3564

Marina BURYAK
Candidate of Pharmaceutical Sciences, Associate Professor at the Department of Drug Technology, National University of Pharmacy, marinaburjak@gmail.com
ORCID: 0000-0002-6671-9662

Viktoriia PUL-LUZAN
Candidate of Pharmaceutical Sciences, Associate Professor at the Department of Drug Technology, National University of Pharmacy, pulluzanv@gmail.com
ORCID: 0000-0001-9553-1143

Tetiana KOVALYOVA
Candidate of Pharmaceutical Sciences, Associate Professor at the Department of Drug Technology, National University of Pharmacy, tatyko72@gmail.com
ORCID: 0000-0002-5984-6196

Volodymyr KOVALYOV
Doctor of Philosophy in Pharmacy, Associate Professor at the Department of Drug Technology, National University of Pharmacy, volodyakw@gmail.com
ORCID: 0000-0003-1603-2771

MODERN METHODS OF STANDARDIZATION OF HOMEOPATHIC MEDICINES IN UKRAINE AND IN THE WORLD

The article considers the requirements of regulatory documentation for the standardization and quality of homeopathic medicines and the possibility of their use in a homeopathic pharmacy.

Purpose. *Conduct a problem-target analysis and summarize data on standardization of homeopathic medicines and determine promising directions of homeopathic pharmacy in Ukraine.*

Methods: *information and search, structural and logical, comparison, generalization.*

Results. *The main priority direction of the state policy of Ukraine in the sphere of providing the population with medicines is to ensure the availability of affordable, high-quality medicines on the pharmaceutical market. Homeopathic medicine has repeatedly proven its effectiveness in the treatment of a wide range of diseases, so there is a constantly growing demand for homeopathic medicines, both in Ukraine and in Europe. Therefore, the safety and quality of homeopathic medicines have become an urgent issue of modern pharmacy and medicine. The quality of homeopathic medicines depends not only on the quality of the manufacturing process, but also on the quality of the raw materials used. Analyzing the regulatory documentation, it was established that if the homeopathic preparation includes active substances in low potencies, they can be analyzed according to the «identification» indicator, if in high potencies, it is recommended to evaluate homeopathic medicinal preparations according to organoleptic and general quality indicators characteristic of this species medicinal form, or apply a clinical quality control method. Differences in the quality control of various homeopathic medicinal forms were revealed during the analysis and generalization of data from homeopathic pharmacopoeias of different countries of the world.*

Conclusions. *For the production of high-quality and safe final products, it is necessary to develop a specialized regulatory document – the Ukrainian Homeopathic Pharmacopoeia, which will help unify the requirements for the quality of homeopathic medicines.*

Key words: *standardization, homeopathy, medicine, pharmacopoeia, regulatory documentation.*

Лілія Вишневська, Світлана Олійник, Марина Буряк, Вікторія Пуль-Лузан, Тетяна Ковальова, Володимир Ковальов. СУЧАСНІ МЕТОДИ СТАНДАРТИЗАЦІЇ ГОМЕОПАТИЧНИХ ЛІКАРСЬКИХ ЗАСОБІВ В УКРАЇНІ ТА У СВІТІ

У статті розглядаються вимоги нормативної документації до стандартизації та якості гомеопатичних лікарських засобів та можливість їх застосування в гомеопатичній аптеці.

Мета. *Провести проблемно-цільовий аналіз та узагальнити дані стосовно стандартизації гомеопатичних лікарських засобів і визначити перспективні напрями гомеопатичної фармації в Україні.*

Методи: *інформаційно-пошуковий, структурно-логічний, порівняння, узагальнення.*

Результати. *Основним пріоритетним напрямком державної політики України у сфері забезпечення населення лікарськими засобами є забезпечення наявності на фармацевтичному ринку доступних, якісних лікарських засобів. Гомеопатична медицина неодноразово довела свою ефективність при лікуванні великого спектру захворювань, тому постійно спостерігається зростаючий попит на гомеопатичні лікарські засоби, як в Україні, так і в Європі. Тому, безпека та якість гомеопатичних препаратів стали актуальним питанням сучасної фармації та медицини. Якість гомеопатичних препаратів залежить не лише від якості проведення технологічного процесу виробництва, а й від якості сировини, що використовується. Аналізуючи нормативну документацію, встановлено що, якщо до складу гомеопатичного препарату входять активні речовини в низьких потенціях, їх можна проаналізувати за показником «ідентифікація», якщо у високих потенціях, то гомеопатичні лікарські препарати рекомендовано оцінювати за органолептичними та загальним показниками якості, характерними для даного виду лікарської форми, або застосовувати клінічний метод контролю якості. Виявлено відмінності у контролі якості різних гомеопатичних лікарських форм під час аналізу та узагальнення даних гомеопатичних Фармакопей різних країн світу.*

Висновки. *Для виробництва якісної та безпечної готової продукції необхідно розробити спеціалізований нормативний документ – Українську Гомеопатичну Фармакопею, яка допоможе уніфікувати вимоги до якості гомеопатичних лікарських засобів.*

Ключові слова: *стандартизація, гомеопатія, лікарський засіб, фармакопея, нормативні документи.*

Introduction. Homeopathic medicines have been used effectively for many decades. Despite the significant progress of modern organic chemistry, which ensures the production of high-quality synthetic biologically active substances, the popularity of homeopathic medicines throughout the world is constantly growing, which is due to their mild effect and the practical absence of side effects and addiction [1].

Homeopathic treatment's place and regulations in the health care system vary from country to country, but the use of homeopathic medicines as over-the-counter medicines is increasing in many parts of the world. Europe remains the largest consumer of homeopathy (Fig. 1). The growing demand for homeopathic medicines can be explained by the fact that the homeopathic method of treatment has long proven its effectiveness in the fight against a wide range of diseases. The production volume of homeopathic medicines in the world has grown almost 10 times over the past 20 years [2].

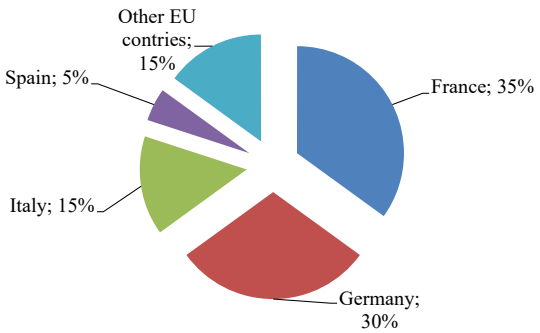

Fig. 1. The level of consumption of homeopathic medicines in different countries

Serial production of homeopathic drugs in Ukraine is currently carried out by the following manufacturing companies: CJSC «National Homeopathic Union» (Kyiv), LLC «Homeopathic Firma «Peak Crimea» (Sevastopol), "Homeopathic Pharmacy" (Kharkiv, Kyiv, Odesa, Ternopil, Uzhhorod, Lviv, Chernihiv, Lutsk), «Lucky-Pharma» LLC (Kyiv). Today, domestic manufacturers ensure that the assortment of the pharmaceutical market is filled with more than 170 homeopathic drugs. Industrial homeopathic drugs enter the pharmaceutical market of Ukraine from well-known global manufacturers. The main import of complex homeopathic medicines to Ukraine is carried out by foreign companies: Germany (DHU, Neel, Vionogisa, Nomvioga, Dr. Taiss), Austria (R. Vitneg), the USA (Votanisal Laboratories Inc.) and France (Boiron) (Fig. 2) [2].

Given the worldwide increase in the use of homeopathic medicines by the population and the rapid expansion of the global market, the safety and quality of homeopathic medicines have become a pressing issue for health authorities, the pharmaceutical industry and consumers. The safety of homeopathic medicines mainly depends on their quality. The requirements and quality control methods for finished homeopathic medicines are much more complex than for chemical preparations, especially for combined or complex homeopathic medicines. In addition, the quality of homeopathic medicines depends on both the quality of the manufacturing process and the quality of the raw materials used [3].

The purpose of the article. Conduct a problem-target analysis and summarize data on standardization of homeopathic medicines and determine promising directions of homeopathic pharmacy in Ukraine.

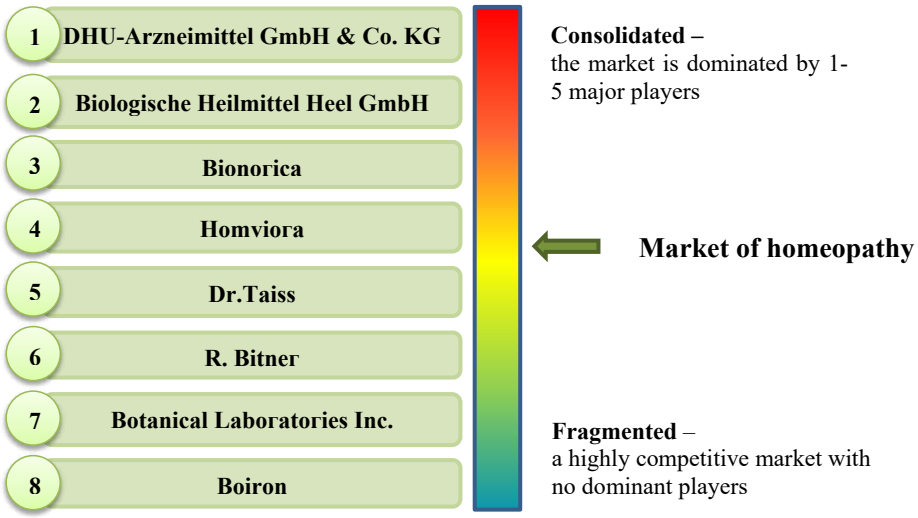

Fig. 2. Leaders of the pharmaceutical market of homeopathic medicines

Methods of the research: information and search, structural and logical, comparison, generalization.

Research results. One of the most urgent problems today in the field of pharmacy is the standardization of medicines, including homeopathic medicines.

The development of homeopathy in all member states of the European Union was facilitated by the change in European pharmaceutical legislation in 2004, in particular, mutual recognition of registration (MRP – manufacturing resource planning) with reference to Directive 2001/83/EC for medicinal products that have already been have a registration certificate in one member state and a decentralized procedure that allows the EU member state to legalize the use of drugs, including homeopathic ones, registered in another EU country [2; 4].

The legislative act relating to homeopathic medicines was put into effect by the European Union back in 1992 and by the European Pharmacopoeia Commission (EPC) in 1996. According to the requirements of the European Community (EU Directives 75/318 EEC, 92/73 EEC, 92 /74 EEC and Directive 2001/83/EC of the European Parliament and of the Council dated 6.11.2001 «On the principles of the European Community regarding medicinal products indicated for human use», homeopathic preparations must meet the same requirements as licensed pharmacotherapeutic agents, however, in relation to the first, there are no requirements for proof of effectiveness [5].

The resolution on folk medicine adopted by the World Health Assembly (WHA) in May 2009 (WHA 62.13) calls on EU member states to «Formulate policies, regulations and standards as part of a comprehensive national health care system to promote adequate, safe and effective use of folk medicine» [6].

Due to the specific nature of homeopathic medicinal products, some quality control methods and test systems that are mandatory in pharmaceutical regulation may sometimes not be applicable. These include identification and quantification of the active substance and toxicological testing of the final homeopathic product. Therefore, in homeopathic pharmacies, to control the quality of drugs in low potencies, a number of less informative tests are performed, for example, visual and organoleptic analysis or simple chemical tests [7].

However, the homeopathic matrix tincture can be diluted well above the level at which molecules of the substance can be found. For high potencies, there are no quantitative methods of determination at all. There-

Table 1

Results of clinical trials of homeopathic medicines

№	Dose of homeopathic medicine	Symptoms after taking one dose of homeopathic medicine
1	one dose of homeopathic medicine in potency from Θ to C30	symptoms appear from one organ to which this drug is tropic
2	one dose of homeopathic medicine in potency from C30 to C1000	symptoms appear from one functional system or the whole body
3	one dose of homeopathic medicine in potency from C1,000 to C50,000	the subject had clear behavioral and mental symptoms
4	one dose of homeopathic medicine in basic potency	symptoms appear within the first 12 hours after taking and last for a short time (from a few minutes to an hour)

fore, only the clinical method of quality control of homeopathic medicines, which was developed by the founder of homeopathy as a method of therapy, Samuel Hahnemann, can be used to determine the quality of highly dynamic homeopathic medicines [8; 9].

The basis of the method of clinical quality control of homeopathic medicines is based on the results of the analysis of drug test protocols (Table 1).

When the patient takes a correctly selected and calibrated homeopathic medicine, the initial reaction should appear mostly within the first hour. Sometimes, if the patient's body is weakened or he needed a higher potency of the homeopathic medicine, the initial reaction appears within the first 12 hours. The symptoms of the initial reaction should last for a few minutes, no more than an hour. If the initial reaction occurs later (after 12 hours from the moment of taking the drug) and lasts longer than one hour, then an uncalibrated homeopathic drug was used, that is, its potency does not correspond to the basic one [9].

The clinical method of quality control of homeopathic medicines is effective and very revealing. If homeopathic pharmacies pay due attention to the issues of product quality, then they necessarily cooperate with homeopathic physicians of the classical school to organize serial testing of finished products [8].

Analyzing data from foreign homeopathic pharmacopoeias and other regulatory documentation, differences in quality control of various medicinal forms used in homeopathy and allopathy were revealed [10; 11–15].

For example, in homeopathic granules, in addition to traditional indicators (description, identification, size of granules, loss in mass during drying, disintegration, dissolution, microbiological purity, quantitative determination, weight of the contents of the container), the number of granules in 1.0 g is also determined [10; 12].

Specific for homeopathy is such a medicinal form as trituration, in which the following are determined: description, identification, homogeneity of mixing (normalized in triturations containing coal, graphite, colored medicinal substances), microbiological purity, weight of the contents of the container. The quantitative content of poisonous and potent substances is carried out only up to the fourth decimal dilution, according to regulatory documentation. Also, liquid and soft dosage forms for use in homeopathy have their own specific features of quality control [10; 11–15].

Determination of the quality of manufactured homeopathic medicines is carried out in accordance with the basic requirements determined by the Ministry of Health of Ukraine and establishing the procedure for quality control of homeopathic medicines in homeopathic pharmacies. They include the evaluation of production documentation, all types of intra-pharmacy quality control of homeopathic medicines and detection of any deviations. In addition, due to the limited possibility (in some cases, the impossibility) of qualitative and quantitative control of finished products, special attention is paid to the training of personnel in a homeopathic pharmacy, which is adapted to the practice of self-control and self-checking at all stages of the production of homeopathic drugs [1; 16; 17].

The analysis of the data of various pharmacopoeias showed that the most complete information on homeopathic medicines is presented in the German Homeopathic Pharmacopoeia, which contains monographs on raw materials of plant, animal and mineral origin for the manufacture of homeopathic medicines. It also describes the methods of preparation of various dosage forms and their quality control. The French homeopathic pharmacopoeia contains 300 monographs and a description of the methods of preparation of homeopathic medicines (Table 2) [13; 14].

Table 2

Availability of articles on homeopathic medicines in pharmacopoeias

№	Pharmacopoeia	General articles	Monographs
1	European Pharmacopoeia	7	35
2	French Homeopathic Pharmacopoeia	-	more than 300
3	German Homeopathic Pharmacopoeia	56	about 580
4	Pharmacopoeia of the United States	-	about 1350
5	State Pharmacopoeia of Ukraine	7	15

There is no separate homeopathic pharmacopoeia in Ukraine, but the State Pharmacopoeia of Ukraine (2.0 edition) includes 7 general articles on homeopathic medicines and 15 monographs on raw materials of mineral origin for homeopathic medicines [10].

The European Pharmacopoeia contains methods of preparing matrix tinctures and individual monographs on homeopathic raw materials. As for the quality control of homeopathic medicines, the standards set out in the European Pharmacopoeia can be considered as a benchmark. It contains a whole list of methods of quantitative and qualitative determination of biologically active substances, there is a separate section «Homeopathic preparation». The section contains general and private pharmacopoeial articles that regulate the quality indicators of raw materials and drugs that are used exclusively for homeopathic purposes; identification of homeopathic medicinal plant raw materials is carried out with the help of macroscopic and microscopic analyses. If necessary, additional tests are carried out (for example, high-performance liquid and thin-layer chromatography). If possible, quantitative determination of

biologically active substances is carried out using appropriate methods. For homeopathic matrix tinctures, perform at least one thin-layer chromatography identification test [25; 12].

Conclusions. The production of homeopathic medicines is carried out in accordance with the requirements of good manufacturing practice, which are part of the quality assurance system. Standardization of homeopathic preparations is ensured by the use of certified raw materials, quality control of each stage of production, compliance with the technological process, standardization according to the dosage form. During the manufacture of homeopathic preparations in high potencies, difficulties may arise in carrying out quality control of finished products. Therefore, the quality and safety of such homeopathic medicines is ensured only by the clinical method of quality control. In foreign homeopathic pharmacopoeias, there are differences in quality control and standardization of various homeopathic medicinal forms. The most complete information on the standardization of homeopathic medicines is given in the German Homeopathic Pharmacopoeia and the European Pharmacopoeia. Therefore, in order to create a high-quality and safe finished product in our country, it is necessary to develop specialized regulatory documentation, namely the Homeopathic Pharmacopoeia of Ukraine, which will help unify the requirements for the quality of homeopathic medicines.

Bibliography:

1. Чекман І. С., Мощич О. П. Гомеопатія, як піонер наномедицини. *Український гомеопатичний щорічник*. 2017. Т. 14. С. 169–175.

2. Use of complementary and alternative medicine in Europe: Health-related and sociodemographic determinants / L. M. Kemppainen et al. *Scandinavian journal of public health*. 2018. № 46 (4). P. 448–455.

3. Tarbell J. A. Homoeopathy simplified. HardPress, 2020. 404 p.

4. Against all odds–the persistent popularity of homeopathy / C. Cukaci et al. *Wiener klinische Wochenschrift*. 2020. Vol. 132, № 9-10. P. 232–242.

5. Guide for the elaboration of monographs on homoeopathic preparations. European Directorate for the Quality of Medicines and Healthcare. Edition 2022 – *European Directorate for the Quality of Medicines & HealthCare*. URL: https://www.edqm.eu/documents/52006/285786/Guide+for+the+elaboration+of+monographs+on+homoeopathic+preparations.pdf/ad6f18d8-07f7-dcfb-fdf2-8ed096bd0ff5?t=1656573388037 (date of access: 12.01.2024).

6. Wrześniewska-Wal I. Traditional and academic medicine – around the WHO strategy. *Journal of Education, Health and Sport*. 2022. Vol. 12, № 11. P. 198–205.

7. Технологія гомеопатичних лікарських засобів : практикум для здобувачів вищ. освіти спец. 226 Фармація, пром. Фармація / Л. І. Вишневська та ін. ; ред. Л. І. Вишневська. Харків : НФаУ, 2023. 142 с.

8. Hahn R. G. Homeopathy: meta-analyses of pooled clinical data. *Forsch Komplementmed*. 2013. № 20 (5). P. 376–381.

9. Rutten L., Rutten M., Manchanda R. K. Fundamentals of statistics and clinical research in homeopathy. Jain Publishers Pvt. Limited, B., 2020. 276 p.

10. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». 2-е вид. Х. : ДП «Український науковий фармакопейний центр якості лікарських засобів», 2014. Т. 3. 732 с.

11. British Pharmacopoeia 2020 [print Edition]. British Pharmacopoeia Commission: The Stationery Office, 2019. 6700 p.

12. European Pharmacopoeia. 10th ed. Strasbourg: Directorate for the Quality of Medicines, Council of Europe, 2019. Vol. 1. 4312 p.

13. German Homoeopathic Pharmacopoeia, Deutscher Apotheker Verlag. 5th ed. CRC Press, 2003. Vol. 1. 1772 p. URL: https://books.google.com.ua/books/about/German_Homoeopathic_Pharmacopoeia.html?id=ALPLoEMFwwMC&redir_esc=y,%202001 (date of access: 17.01.2024).

14. La pharmacopée française. La 11e édition. Agence nationale de sécurité du médicament et des produits de santé (France): ANSM, Saint-Denis, 2012. URL: https://ansm.sante.fr/documents/reference/pharmacopee/la-pharmacopee-francaise (date of access: 17.01.2024).

15. The Homoeopathic Pharmacopoeia of the United States. American Institute of Homeopathy Commit: Franklin Classics Trade Press, 2018. 682 p. URL: https://www.hpus.com/document/homeopathic-pharmacopoeia-of-the-united-states/ (date of access: 17.01.2024).

16. Treatment of allergic rhinitis: A review of homeopathic therapy / T. Yarnykh et al. *Journal of Advanced Pharmacy Education & Research*. 2023. Vol. 13, Issue 2. P. 107–117.

17. Prevalence of homeopathy use by the general population worldwide: A systematic review / C. Relton et al. *Homeopathy*. 2017. № 106. P. 69–78.