ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Comparative Analysis of Pharmacopeial Requirements to Extemporaneous Medicines

Melnik G.M., Yarnykh T.G., Rukhmakova O. A.*

National University of Pharmacy, Kharkiv, Ukraine.

***Corresponding Author: Rukhmakova O. A.**

Abstract

The article presents a comparative analysis of pharmacopoeial requirements for extemporaneous medicines on the example of the articles of State Pharmacopoeia of Ukraine 2.0 "Nonsterile medicines made in pharmacies" and Guide for the Compounding Practitioner USP on Compounding "795" "Pharmaceutical Compounding-Non-sterile Preparations". These articles have been shown to differ in structure and title, but many sections are close in content. It is established that State Pharmacopoeia of Ukraine contains, to date, a very limited list of general pharmacopoeial articles for individual extemporaneous dosage forms unlike USP. In this regard, it is necessary to expand and improve the basic regulatory documentation, including general articles of State Pharmacopoeia of Ukraine, in order to improve the quality of extemporaneous medicines.

Keywords: *Analysis, Pharmacopoeia, Requirements, Extemporaneous medicines.*

Introduction

The human body is a complex biochemical system in which the adverse effects of external and internal factors can cause pathological processes of varying severity. For many years, traditional and alternative medicine (allopathy, homeopathy, folk medicine) is based on a single principle of their treatment-a thorough analysis and individual approach to the treatment of the patient, taking into account objective and subjective factors. This principle has always been followed by extemporaneous prescriptions [3]. Extemporaneous medicines contain active ingredients without fillers, preservatives, stabilizers and the like.

The individually selected composition of such medicines allows taking into account the features of the body, the course of the disease, the symptoms of the disease and its stage. In addition, a large number of excipients used in the manufacture of medicines at pharmaceutical companies can cause the development of allergic reactions in most patients. Experience has shown that, despite the growing assortment of ready-to-use medicines, the preparation of medicines in pharmacies by prescription does not lose its value. In addition, among prescriptions for individual preparation coming to pharmacies, many children's dosage forms, where individual combinations of medicinal substances and doses are extremely necessary [8, 10].

It is known that one of the legislative standards governing the manufacture of medicines is the state pharmacopoeia. It includes guidelines for the manufacture, quality control of medicines, determines higher doses of medicinal substances, and sets requirements for medicinal herbs. Compliance with the pharmacopoeial norms and requirements, combined with the GMP standard, ensures the proper quality of the medicinal substances and medicines based on them.

The history of the creation of the first pharmacy collections begins with ancient manuscripts, including the Papyrus by Edwin Smith, the pharmacopoeia of Pliny the Elder, the Garden of Health by Peter Sheffel and more. The first pharmacopoeia was issued in 1498 in Florence under the name "Ricettario Fiorentino". To date, many countries in the world have their own pharmacopoeias.

The World Health Organization publishes International Pharmacopoeia, but it does not have a legislative nature unlike national (state) pharmacopoeias. In countries that do not have their own pharmacopoeias, they use international, European or other [7].

Thus, United States Pharmacopoeia is used in the United States of America, British Pharmacopoeia in Great Britain. In Germany, there are three pharmacopoeias at once: German (DAB, Deutsches Arzneibuch), European (PhEur, Europäisches Arzneibuch) and German Homeopathic (HAB, Homöopathisches Arzneibuch). In Ukraine, State Pharmacopoeia was first issued in 2001. Subsequently, in 2004, 2008, 2009 and 2011, relevant additions to the first edition of State Pharmacopoeia of Ukraine (SPU) appeared which were fully harmonized with the European Pharmacopoeia.

The second edition of SPU was developed in 2014 and contained three volumes. To date, three additions to the second edition have already been issued [2]. The regulation of extemporaneous medicines technology in many countries of the world is also reflected on the pages of state pharmacopoeias. The objective of this work is to conduct a comparative analysis of pharmacopoeial requirements for technology and quality control of extemporaneous medicines.

Materials and Methods

Comparative analysis of pharmacopoeial requirements was carried out by conventional empirical methods using informational materials, in particular, pharmacopoeias, data from literature and own research materials.

Results and Discussion

It is known that the only international pharmacopoeial standard that defines the requirements for technology and quality control of medicines today is European Pharmacopoeia. However, in the current editions it does not contain separate monographs on extemporaneous medicines [5].

In contrast to European Pharmacopoeia, about 120 monographs on extemporaneous medicines are included in British Pharmacopoeia, most of which are devoted to pharmaceutical production of soft, solid and liquid dosage forms [4]. Swedish and Belgian pharmacopoeias also contain significant information on extemporaneous medicines technology. Thus, the national part of Swedish Pharmacopoeia standardizes standard procedures for the preparation of extemporaneous medicines and medicines "in stock". In addition, it contains 130 monographs for medicines for small-scale production in pharmacies and an application that regulates the requirements for intra-pharmaceutical products. There is also an application in Belgian Pharmacopoeia, in accordance with which the preparation of extemporaneous medicines is carried out [7].

However, in comparison with other leading pharmacopoeias of the world, the Pharmacopoeia of the USA has the most important informative material on preparation and quality control of medicines in the conditions of pharmacies. A separate edition of this pharmacopoeia entitled "USP Pharmacists Pharmacopoeia" is devoted only to the issues of extemporaneous medicines manufacturing. "USP Pharmacists Pharmacopoeia" (2008-2009 edition) contains general pharmacopoeial articles on extemporaneous medicines: "1161" "Pharmacy compound practices", "1191" "Stability considerations in dispensing practice", "1206" "Sterile drug products for home use", "1162" "Prescription balances and volumetric apparatus", etc. [9].

In 2014, a supplement to the "USP Pharmacists Pharmacopoeia" (2008-2009 edition) was published under the title "Guide to the Compounding Practitioner USP on Compounding". The second section of this issue of Compounding-Related General Chapters contains 5 updated general pharmacopoeial articles on extemporaneous medicines technology:

- "795" "Pharmaceutical Compounding- Nonsterile Preparations";
- "797" "Pharmaceutical Compounding-Sterile Preparations";
- "1160" "Pharmaceutical Calculations in Prescription Compounding";
- "1163" "Quality Assurance in Pharmaceutical Compounding";
- "1176" "Prescription Balances and Volumetric Apparatus" [6].

Until 2001, standards for extemporaneous medicines technology and quality control in Ukraine were reflected only in relevant orders of the Ministry of Health of Ukraine. Some guidelines for the preparation of indi-

vidual extemporaneous dosage forms have begun to appear in general articles of State Pharmacopoeia of Ukraine since 2001. In 2008, section 5.N.1 was included in SPU 1.2. "Extemporaneous Medicines" with a block of general articles on the preparation and quality control of non-sterile medicines in pharmacies.

However, it did not contain requirements for general rules for the technology of individual dosage forms. Subsequently, in 2011, the pharmacopoeial article "Powders made in pharmacies" was introduced in SPU 1.4, and in 2014, a second edition of SPU was published, the third volume of which contained a separate section on extemporaneous medicines (Table 1).

Table 1: Pharmacopoeial articles on extemporaneous medicines in SPU

Title	Authors	The level of implementation
5.N.1 "Extemporaneous Medicines" ("Nonsterile medicines made in pharmacies")	Chernykh V. P., Tikhonov O. I., Yarnykh T. G. et al.	Included in SPU 1.2, 2008, p. 206; included in SPU 2.0, vol. 3, 2014, p. 697
"Powders made in pharmacies"	Yarnykh T. G., Chushenko V. M. et al.	Included in SPU 1.4, 2011, p. 221; included in SPU 2.0, vol. 3, 2014, p. 710
"Soft medicines made in pharmacies"	Yarnykh T. G., Tikhonov O. I., Rukhmakova O. A. et al.	Included in SPU 2.0, vol. 3, 2014, p. 707
"Suppositories and pessaries made in pharmacies"	Yarnykh T. G., Tikhonov O. I., Rukhmakova O. A. et al.	Included in SPU 2.0, vol. 3, 2014, p. 716

In our opinion, it is interesting to compare the requirements for extemporaneous medicines technology and quality control according to the articles of State Pharmacopeia of Ukraine 2.0 "Nonsterile medicines made in pharmacies" (2014) and the Guide for the Compounding Practitioner USP on Compounding "795" "Pharmaceutical Compounding-Nonsterile Preparations (2014), the structure of which is given in Table 2. As can be seen from the Table 2, the indicated pharmacopoeial articles differ in structure and title, but many of their sections are close in content. Thus, the SPU article defines extemporaneous medicines as "medicines made under the prescription of a physician for a particular patient or at the request of a health care facility". Article of USP as "prepared in the pharmacy on prescription medicines or dietary supplements, or carriers for medicinal substances" [2]. It should be noted that the introduction to USP "795" states that extemporaneous medicines manufacturing is an integral part of the pharmaceutical and healthcare sectors in general. In this case, the preparation of extemporaneous medicines is conditionally divided into three categories (categories of extemporaneous medicines preparation).

Table 2: the structure of articles on the preparation of nonsterile extemporaneous medicines by SPU 2.0 and Guide for the Compounding Practitioner USP on Compounding

SPU 2.0 "Nonsterile medicines made in pharmacies"	Guide for the Compounding Practitioner USP on Compounding "795" "Pharmaceutical Compounding – Nonsterile Preparations"
• Definition • Active substances and excipients • Preparation • Quality control (intra-pharmacy control) • Packaging • Labelling • Storage • Intra-pharmacy products: *definition, concentrated solutions, semi-finished products, stock-based medicines*	• Introduction • Definition of basic terms and concepts • Categories of extemporaneous medicines preparation • Responsibility of the pharmacist for the preparation of extemporaneous medicines • Technological process • Premises • Equipment • Selection of accessory materials, handling and storage • Extemporaneous medicines stability criteria and shelf life • Packaging, containers • Documentation • Quality control

	• Recommendations to patients • Certification training • Preparation of extemporaneous medicines for animals

The criteria for determining a category are as follows:

- Complexity of the technological process;
- Available information on the stability of extemporaneous medicines components;
- Packaging and storage requirements;
- Dosage form;
- Complexity of calculations;
- Local or systemic action of extemporaneous medicines;
- The potential risk of side effects for the patient.

The simple category is the preparation of a medicine for which a corresponding USP monograph or article in a peer-reviewed journal exists, clearly describing the quantities of all prescription components, process, equipment, stability and shelf life data; or the preparation of an extemporaneous medicine from a finished industrial medicine by combining it with additional components.

The middle category is the preparation of a medicine that requires special calculations or procedures to determine the amount of ingredients for a particular extemporaneous medicine (e.g., drop calibration); or preparation of extemporaneous medicine for which ingredients are lacking in stability data. *The difficult category* is the preparation of a medicine that requires special qualifications, equipment, technological operations and more. For example, the preparation in the conditions of pharmacies transdermal dosage forms, medicines with modified release of medicinal substances, as well as some suppositories of systemic action.

It is the responsibility of the pharmacist for the preparation of extemporaneous medicines to ensure that they have the appropriate professional skills and are constantly expanding their knowledge by participating in special seminars and / or studying required literature [6]. The section "Technological process" of article "795" lists the criteria that must be strictly observed in the extemporaneous preparation of medicines. Thus, it is known that active pharmaceutical ingredients and excipients are used for the preparation of medicines.

According to the Guide for the Compounding Practitioner, substances that meet USP requirements or manufacturers specifications are preferred for the preparation of all medicines. It should be noted that as active ingredients USP allows the use of medicines of industrial production, which are contained in the packs with the expiry date. In Ukraine, according to the current documents, it is also allowed to use ready-made medicines for the preparation of extemporaneous medicines.

Thus, the SPU article states that ready-to-use medicines can be used in the preparation of oral extemporaneous medicines or extemporaneous medicines for external use, unless indicated by a physician in the prescription. A compulsory element of extemporaneous medicines preparation is the maintenance of the necessary documentation, including written records known in Ukraine under the name "written control passport".

The article of SPU in the section **"**Preparation" contains the following provisions: "Before preparing extemporaneous medicines, check the correctness of the formulation, prescription and compatibility of ingredients, check the doses and norms of release, calculate the number of active and auxiliary substances on the back of the written control passport, select technology of extemporaneous medicine, select appropriate packaging means, depending on the aggregate condition, properties, volume or weight of extemporaneous medicine".

In addition, the text of this section indicates the rules for dealing with medicinal substances, depending on their physical and chemical properties. Information on the rules of technology can also be found in the guideline "Requirements for the preparation of nonsterile medicines" approved by the Ministry of Health of Ukraine, which contains instructions for the preparation of solid, liquid, soft dosage forms in pharmacies [1].

In the case of medicines prepared "in stock" according to the article of SPU, their technology and equipment must be indicated in the technological instructions. The USP on Compounding Guide "795" "Pharmaceutical Compounding - Nonsterile Preparations" article contains separate sections entitled "Premises" and "Equipment". There are no relevant sections in the SPU article, but there are general guidelines on the conditions of preparation and equipment. More information on this issue can be found in the guide [1].

The section of article "795" "Quality control" has the following meaning: "The safety, quality and pharmacological action of extemporaneous medicines depend on the ingredients selected and the calculations made, the exact measurements and conditions of manufacture. The pharmacist should monitor every procedure in the manufacturing process".

In fact, it is a written and interrogative control that operates in Ukraine. In the article of SPU "Nonsterile medicines made in pharmacies" in the section **"**Quality control" it is stated that extemporaneous medicines are subject to intra-pharmacy control: written, interrogative, organoleptic, physical, chemical and on-leave control. Here are also the rules of intra-pharmacy control of extemporaneous medicines. It should be noted that these sections differ in volume and content.

The sections of SPU 2.0 and USP on Compounding's Guide to Compounding Practices on Packaging and Labelling of extemporaneous medicines are almost indistinguishable. The choice of packaging is made taking into account the properties, purpose and quantity of the medicine. There are some differences regarding the terms of storage of extemporaneous medicines.

According to USP, for liquid aqueous dosage forms for internal use (oral fluids), the shelf life is not more than 14 days (provided they are stored in a cool place). For all other dosage forms, the expiry date should not exceed 30 days or 6 months in the presence of scientifically validated information on the stability of each individual ingredient of the prescription. The following terms of extemporaneous medicines are indicated in the article of SPU: emulsions and suspensions-3 days; infusions, decoctions and mucus-2 days; aqueous oral medicines-no more than 14 days when stored in a cool place; aqueous solutions for external use-no more than 30 days; others-10 days or, with scientifically validated information on the stability of each ingredient of the prescription, not more than 6 months.

Patients should be advised of correct use, storage, and signs of medicine instability when dispensing an extemporaneous medicine according to the section "Recommendations for Patients" of article "795". A separate section of article "795" deals with the production of extemporaneous medicines for animals. Particular attention is paid to the toxic effects of active pharmaceutical ingredients on animals in the text of this section.

Thus, based on the analysis of the pharmacopoeial requirements for extemporaneous medicines, it can be argued that the pharmacopoeial articles of SPU 2.0 and USP on Compounding's Guide to the Compounding Practice have differences in structure and title, but many of their sections are close in content. However, it should be noted that SPU currently contains a very limited list of general pharmacopoeial articles for some extemporaneous dosage forms unlike USP. In this regard, the work of scientists of National University of Pharmacy on the creation of general SPU articles continues (Table 3).

Table 3: List of developed pharmacopoeial articles on extemporaneous medicines

Title	Authors	The level of implementation
"Suspensions made in pharmacies"	Yarnykh T. G., Tikhonov O. I., Melnik G. M. etc.	submitted to the Pharmacopoeial Center for review
"Emulsions made in pharmacies"	Yarnykh T. G., Tikhonov O. I., Melnik G. M. etc.	submitted to the Pharmacopoeial Center for review
"Infusions and decoctions made in pharmacies"	Yarnykh T. G., Tikhonov O. I., Melnik G. M. etc.	submitted to the Pharmacopoeial Center for review
"Pharmaceutical incompatibilities"	Yarnykh T. G., Tikhonov O. I, Rukhmakova O. A., Melnik G. M.,	submitted to the Pharmacopoeial Center for review

	Dankevich O. S.	
"Ensuring stability of extemporaneous medicines"	Yarnykh T. G., Tikhonov O. I, Rukhmakova O. A., Melnik G. M., Dankevich O. S.	submitted to the Pharmacopoeial Center for review

Expanding and improving basic regulatory and technical documentation, which is of a legislative nature, in particular through the development of general articles of the SPU, will significantly improve the quality of medicines manufactured in pharmacies

Conclusions

- A comparative analysis of pharmacopoeial requirements for technology and quality control of extemporaneous medicines was conducted on the example of articles of State Pharmacopoeia of Ukraine 2.0 "Nonsterile medicines made in pharmacies" and the Guide for the Compounding Practitioner USP on Compounding "795" "Pharmaceutical Compounding-Nonsterile Medicines". These articles have been shown to differ in structure and title, but many sections are close in content.

- It is established that SPU contains, to date, a very limited list of general pharmacopoeial articles for individual extemporaneous dosage forms unlike USP. In this regard, it is necessary to expand and improve the basic regulatory documentation, including general articles of SPU, in order to improve the quality of extemporaneous medicines.

References

1. Requirements for the preparation of nonsterile medicines in pharmacies: instruction ST-N MH 42-4.5:2015 – K.: MH of Ukraine, 2015. – 117 c.
2. State Pharmacopoeia of Ukraine: Nonsterile medicines made in pharmacies / The state enterprise "Scientific Expert Pharmacopoeial Center". – 2 ed. – Kh. : RIREG, 2014. – p. 697-707.
3. The principles of preparation medicines in pharmacies / T. G. Yarnykh, O. I. Tikhonov, O. A. Garkavtseva, N. V. Romanenko // Provisor. – 2009. 21: 9-15.
4. British Pharmacopeia (2019) London, UK: TSO, 6648.
5. European Pharmacopoeia (2017) 9-th ed. Strasbourg: Council of Europe, 4016.
6. Guide for the Compounding Practitioner USP on Compounding. -Rockville: The United State Pharmacopeial, 2014. 375.
7. Kochanowska-Karamyan AJ (2016) Pharmaceutical Compounding: the oldest, most symbolic, and still vital part of pharmacy / A. J. Kochanowska-Karamyan // Int. J. of Pharm. Compound, 20 Is. (5): 367-374.
8. Methodology for development of pediatric medicines for complex treatment of diseases of immune-dependent nature / O. A. Rukhmakova, T. G. Yarnykh, O. I. Tykhonov, A. A. Kotvitska // Journal of Global Pharma Technology. – 2018 10(12): 54-57.
9. USP Pharmacists Pharmacopeia (2008) II ed. – Rockville: The United State Pharmacopeial, 15-19.
10. Yarnykh TG (2015) Peculiarities of the technology, quality control, and pharmaceutical development of extemporaneous preparations for children / T. G. Yarnykh, O. A. Rukhmakova // Pharmaceutical Chemistry Journal, 49, Is. (2): 122-124.

