CZU 615.322.07+615.11

COMPARATIVE ASSESSMENT OF PHARMACOPOEIA REQUIREMENTS REGARDING THE STANDARDIZATION OF HERBAL DRUGS

Cornelia FURSENCO [1,3], Elena-Andrea DRĂGĂLIN[2], Tatiana CALALB[1], Livia UNCU[2,3]

[1]Department of Pharmacognosy and Pharmaceutical Botany
[2]Department of Pharmaceutical and Toxicological Chemistry
[3]Scientific Center of Drugs
Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Correspondent author*: cornelia.fursenco@usmf.md

Rezumat

EVALUAREA COMPARATIVĂ A CERINȚELOR FARMACOPEICE PRIVIND STANDARDIZAREA PRODUSELOR VEGETALE

Medicamentele de origine vegetală au fost folosite în întreaga lume de secole. În ultimele decenii, datorită solicitării și utilizării în creștere la nivel global a medicamentelor pe bază de plante medicinale, controlul calității acestor produse este foarte important. În acest review este analizat comparativ cadrul legal actual de reglementare al produselor vegetale medicinale în diferite țări și metodele de asigurare a calității ace stora în conformitate cu standardele farmacopeice. Aducem o scurtă descriere a farmacopeilor analizate, inclusiv și evaluarea cerințelor de standardizare pentru produse vegetale descrise în monografiile farmacopeice individuale. Evaluarea farmacopeilor (Farmacopeea Europeană, Farmacopeea Statelor Unite, Farmacopeea de Stat a Federației Ruse și Farmacopeea Română), denotă că cerințele pentru standardizarea produselor vegetale sunt în mare parte similare, cu referire la teste interdependente ce oferă o caracterizare completă a controlului calității în privința identității, purității și conținutului principiilor active, dar menționăm și mici excepții.

Cuvinte-cheie: produs vegetal, standardizare, farmacopee, controlul calității.

Abstract

Herbal medicines have been used worldwide for centuries. Thanks to the globally increasing application of herbal medicines in the last decade, quality control of the drug products derived from medicinal plants is very important. The comparison of current regulatory framework of herbal products in different countries and the quality assurance by compliance with pharmacopeial standards is illustrated in this study with a brief description of the analyzed pharmacopoeias, including review of the standardization requirements illustrated in herbal drugs monographs. The requirements were evaluated of: The European Pharmacopoeia, The United States Pharmacopoeia, The State Pharmacopoeia of the Russian Federation, and The Romanian Pharmacopoeia, which contain similar science-based quality standards (with some small exceptions) and include multiple interrelated tests to provide a full quality characterization for each herbal drug in terms of its identity, purity, and content of active principles.

Keywords: herbal drug, standardization, pharmacopoeia, quality control.

INTRODUCTION

Throughout the history, medicinal plants have been used therapeutically all around the world, nowadays, being an important aspect of the modern medicine system. According to an estimate of the World Health Organization (WHO), about 80% of the world population still uses herbs and other traditional medicines for their primary health care needs [1, 2].

Today we live in a globalized world where medicinal products – including herbal drugs and herbal medicines – are produced and distributed all around the world [3].

With the ever-increasing use of herbal medicines and the global expansion of the herbal medicines market, safety has become a major concern for both health authorities and the public in many countries. The quality of herbal medicines has a direct impact on their safety and

efficacy. There are many control measures for herbal medicines, and the first important step is to control the quality of medicinal plants and herbal drugs. The scientific evaluation of safety and efficacy of herbal drugs and herbal medicines is thus of vital importance from both medicinal and economic perspectives [1, 4].

MATERIALS AND METHODS

As analyzed documents, data from four pharmacopoeias (Ph. Eur. 10.0, USP 2022, the 14th edition of SPRF and the RPh X) and their official websites, the official websites of the WHO, European Medicines Agency (EMA), The European Scientific Cooperative on Phytotherapy (ESCOP), U.S. Food and Drug Administration (FDA), and WHO guidelines in the field of herbal medicines regulation were analyzed. To identify relevant studies, the following database platforms were also used: Medline, PubMed, the Cochrane Methodology Register, Scopus.

RESULTS AND DISCUSSION

Standardization of herbal medicines is the process of prescribing a set of standards or inherent characteristics, constant parameters, definitive qualitative and quantitative values that carry an assurance of quality, efficacy, safety, and reproducibility [2].

In the specialized literature, there are a lot of names referring to the products derived from medicinal plants: herbal drugs or herbal substances (plants parts in an unprocessed, usually dried form, but sometimes fresh), herbal medicinal products or herbal medicines (any medicinal product, exclusively containing as active substances one or more herbal substances/drugs). We will use the herbal drug and herbal medicines terms, that are found and described in the Ph. Eur. and WHO guidelines [1, 3, 5]. Regulatory requirements for the quality of herbal drugs and herbal medicines vary depending on the country and the regulatory category. The same herbal drug or herbal medicine can be marketed as a drug in Europe and as a dietary supplement in the United States. In Europe, herbal drugs and herbal medicines are produced according to quality standards typical for pharmaceutical products. In the United States, herbal medicines can only be marketed as food supplements. Specific health claim of the need FDA approval [6, 7].

The European Union has a complex legislative framework that allows for the use of herbal medicines. Directive 91/507/EEC gives details of quality, safety, and efficacy. Further directives followed, e.g., European Directive 2004/24/EC of 31 March 2004 [8, 9].

Herbal medicines were first included in the WHO International Conference on Drug Regulatory Authorities in 1986 [10]. Also, ESCOP, founded in 1989, has produced several comprehensive monographs. ESCOP and WHO monographs are used in many member states as summaries and sources of bibliographic data. WHO has a set of specific Guidelines for the evaluation of the safety, efficacy and quality of herbal drugs or herbal medicines [11, 12, 13, 14].

The most established information regarding the use of herbal drugs and herbal medicines currently available in the public domain is in the form of pharmacopeial monographs. Pharmacopeial standards provide quality specifications for drugs, excipients, dietary supplements, and herbal medicines, in the form of quality monographs supported by the general chapters and general monographs. The general monographs include tests for elemental contaminants, microbial contaminants, and pesticide residues. Monographs usually comprise sections on definition, identification, composition or assay, and limits on contaminants [9].

Following the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidance on good pharmacopeial practices (GPP) was published in 2016. The primary objective of the GPP is to define approaches and policies in establishing pharmacopeial standards with the goal of harmonization. In line with this objective, this guidance for monographs on herbal medicines has been developed outlining the structure and contents of an herbal medicine monograph. Pharmacopeial monographs for herbal medicines should contain information in the definition that is consistent with the monograph title, followed by specifications for quality including identity, purity, and content [14].

The WHO describes that “a pharmacopoeia is a legally-binding collection, prepared by a national or regional authority, of standards and quality specifications for medicines used in that country or region” [5, 14].

In the given analysis, we will specify the similarities and differences regarding the standardization of herbal drugs in different pharmacopoeias.

European Pharmacopoeia (Ph. Eur.)

The Ph. Eur. is the official book that provides quality standards for the manufacture and control of medicines in Europe and in other countries that utilize Ph. Eur., including Republic of Moldova. It was inaugurated in 1964 through the Convention on the elaboration of a European Pharmacopeia, under the auspices of Council of Europe [3]. The present 11th Edition of the Ph. Eur. is effective from 1 January 2023, but because it is not yet available, the 10th Edition of the Ph. Eur. was used in this review. The Ph. Eur. has kept pace with this development, being today a European single point of reference for the quality of medicines, with a global influence. The Ph. Eur. community has continued to grow in the past years, with the accession of the Republic of Moldova to the Convention in 2017 and the arrival of 3 new observer states (India and Japan in 2016 and the Republic of Uzbekistan in 2018), clearly illustrating the lasting appeal and dynamism of the Ph. Eur. [6].

According to Ph. Eur., an herbal drug is mainly a whole, fragmented, or a cut plant, part of a plant, algae, fungi, or lichen, in an unprocessed state, usually in dried form, but sometimes fresh. The nomenclature of herbal drugs is done according to the binomial system, being defined by the botanical scientific name. The first word indicates genus and/or species and/or variety and the second word defines the type of botanical organ, which can be underground organs (*radix, rhizome, tubera, bulbus*), bark (*cortex*), or aerial organs (*herba, folium, flos, fructus, pseudofructus, pericarpium, semen, seminis tegumentum, gemmae*) [3, 15].

The official texts of more than 2,500 monographs and about 370 general texts in Ph. Eur. 10.0 comprise 6 general monographs (such as herbal drugs, herbal drug extracts, and essential oils); 27 general texts (such as pesticides, heavy metals in herbal drugs, and HPTLC of herbal drugs and herbal drug preparations); and 315 individual monographs. It is important to notice that the general monograph *Herbal drugs* applies to all herbal drugs for medicinal use and its provisions must be considered when elaborating specific monographs [3].

The monographs on herbal drugs have a specific nomenclature, including the following ones that are ilustrated in the table below (table).

Table. **Parameters of herbal drugs standardization in some pharmacopoeias**

Pharmacopoeias	Parameters of herbal drugs standardization
Ph. Eur. 10.0	- Title (English) - Subtitle (Latin, singular) - Definition - Characters - Identification - Tests - Assay - Storage
RPh X	- Title (Latin, singular) - Subtitle (Romanian) - Definition - Description - Identification - Tests - Dosage - Storage - Pharmacological action and uses
14th Edition of SPRF	- Title (Russian) - Subtitle (Latin, plural) - Definition - Authenticity (macro-, microscopic tests) - Tests (quantitative and qualitative) - Packaging, labeling, transportation - Storage
USP 2022	- Title (English, singular) - Definition - Identification - Specific tests - Composition - Additional Requirements (packaging and storage, labeling and USP reference standards)

The first section is monograph *Title* (in English and French in respective versions), followed by a Latin *Subtitle*. The Latin *Title* is derived from the scientific name of the producing plant species. It is formed by the genus

(genitive) and/or species (genitive) names, followed by the name of the organ used (nominative and singular). The second compartment is the *Definition*, where some or all of the following are usually included: the state of the drug (whole, fragmented, peeled, cut, fresh or dried); the complete scientific name of the plant (genus, species, subspecies, variety, author); commonly used synonyms; the part or parts of the plant used (written in the singular); where appropriate, the stage in the growth cycle when harvesting takes place; wherever possible, the minimum content of quantified constituents. The next section is named *Characters* and contains a brief description of the physical characters of the herbal drug, including organoleptic, macroscopic and microscopic botanical features. To the organoleptic characters refers colour and smell of the drug, where this is characteristic. It is important to mention that toxic herbal drugs are not allowed to be tasted. No reference is made to odour unless it is highly characteristic and can be described with reference to independent odours.

The *Identification* compartment includes macroscopic and microscopic characteristics, chemical tests and chromatographic or spectroscopic patterns. Macroscopic characteristics are based on sensory evaluation parameters like shape, size, colour, texture, odour and taste, while the microscopic ones allow to recognize the herbal drug according their known cyto- and histological characters. Monographs may contain schematic drawings of the main microscopic features of powdered drugs. Chemical reactions are included only where TLC/HPTLC does not provide sufficient identification and if the reaction is particularly characteristic of a constituent or group of constituents. Chromatographic fingerprinting can be carried out using techniques such as thin layer chromatography (TLC), High performance thin layer chromatography (HPTLC), High performance liquid chromatography (HPLC), Gas chromatography (GC) and other hyphenated techniques.

The following large compartment is known as *Tests,* which including: Total ash, Ash insoluble in hydrochloric acid, TLC, GC or Liquid chromatography (LC), Foreign matter, Heavy metals, Loss on drying, Pesticides, Water, Swelling index, Bitterness value, Extractable matter and other tests (Starch, Matter insoluble in ethanol, Broken drug, Aflatoxin B1, Ochratoxin A, Radioactive contamination, Microbial contamination, etc.).

Total ash test is always included unless otherwise justified. It is to be carried out on the powdered herbal drug. Ash insoluble in hydrochloric acid test may be carried out depending on the nature of the particular herbal drug and is used to detect unacceptable quantities of certain minerals. TLC can be used under *Tests* to detect plant species that are not part of the definition. The use of GC or LC is indicated to detect plant species that are not part of the definition, to limit certain constituents or to control the possible degradation or evaporation of any constituents that must be present in the drug at a certain level. Foreign matter represents the parts of the producing plant that are not defined as the drug, and foreign elements of herbal origin that are not derived from the plant species given in the definition, or of mineral origin or any other matter not within the definition of the drug. Heavy metals test is prescribed where there is the potential for contamination with heavy metals. A general method *Heavy metals in herbal drugs and fatty oils* is included in the Ph. Eur. Loss on drying test determines the maximum amount of water that may be present in the drug under the stated conditions. Water test is done for herbal drugs containing more than 10 ml/kg (1 per cent) of essential oil, being carried out instead of the test for loss on drying. Swelling index is applicable to certain hydrocolloid-containing herbal drugs, Bitterness value is necessary to herbal drugs containing bitter principles. Extractable matter test is considered useful to determine only in herbal drugs where no constituent suitable for an assay is known or where the material is used to produce a preparation with a dry residue. The *Assay* compartment includes the quantitative determination of the constituent(s) responsible for the therapeutic activity of the herbal drug, if it is known, in case where the chemical constutents(s) responsible for the therapeutic activity is/are not known, it is included testing for determination of the chemical contituent(s) that act as analytical marker(s). Wherever possible, LC or GC are the methods of choice to determine the content of specific constituents rather than a global determination by spectrophotometry.

The *Storage* compartment includes the storage conditions that are described in the general monograph *Herbal drugs,* however, sometimes additional specific conditions are given in the individual monograph [3].

United States Pharmacopoeia (USP)

USP is an independent, scientific, nonprofit public health organization devoted to improving health through the development of public standards. USP's mission is to improve global health through standards and related programs that help ensure the quality, safety, and benefit of medicines and foods [7, 16].

The individual monographs for herbal drugs are included in the Dietary Supplements section (Volume 3). These monographs present a specific nomenclature that reflect the quality control procedures of these products: the *Title* of herbal drug is indicated only in English (singular), in the *Definition* section, it is indicated the complete scientific name of the plant in Latin and the minimum content of quantified constituents (wherever possible). The *Identification* is according to the Specific tests for Botanic characteristics, LC, TLC, HPTLC and HPLC. The following section is *Composition*, that means the dosage of the active substance(s), most often being carried out by the HPLC method. The *Contaminants* section includes the following subsections: Elemental impurities, Pesticide Residue Analysis, Microbial Enumeration tests, Absence of specified microorganisms, Test for Aflatoxins. In the section *Specific tests*, there are included Botanic characteristics (macroscopic and microscopic), Loss on drying, Total ash, Water-soluble extractives, Alcohol-soluble extractives, Foreign Organic Matter. The last section is *Additional Requirements*, which refers to the packaging and storage conditions, labeling and USP reference standards (table) [16].

The Russian Federation's State Pharmacopoeia (SPRF)

The 14th edition of the SPRF was implemented in 2018. In the 14th edition of the modern SPRF, medicinal plants are described in 107 monographs. Altogether, 25 new monographs were included in the 14th edition, and one monograph was excluded in comparison to the 11th edition. Some of the included plants are not endemic to Russia and do not have a history of traditional use, or on the other hand, are widely used in Western medicine [17]. Each monograph of the SPRF contains information including herbal drug name (both Russian and Latin: the first name is indicated in Russian, the second one is Latin, being written in plural form),

recommended collection time, macroscopic evaluation (for whole and pulverized plant material), microscopic observation, quantitative data (Loss of material on drying, concentration of chemical constituents or biological activity), Ash content, Ash content that is insoluble in 10% HCl, broken parts, organic and mineral adulteration, qualitative assay (chemical reactions or chromatography), fraction sieve analysis (for pulverised material), packaging, labeling, transportation and storage conditions (table). Unlike other Pharmacopoeias, the Russian one includes general monographs for each type of herbal drug, namely: *Herba; Folia; Flores; Cortex; Radices; Rhizomata, bulbi, tubera, bulbotubera; Fructus; Semina; Gemmae*, which regulates the quality of these types of herbal drugs and their requirements are mandatory to be respected by the individual herbal drugs included in the SPRF [18].

Romanian Pharmacopoeia (RPh)

The current Edition of the RPh, the 10th, applicable since 1993, consists of 1315 pages, representing a large amount of information and it was accompanied by 3 supplements: I (2000, 154 pages), II (2004, 313 pages) and III (2006, 370 pages). Regarding herbal drugs, the number of monographs was considerably reduced, unlike the previous editions: 48 herbal drugs, 34 being indigenous and 14 – imported ones. It is important to note that the number of medicinal plants included in various editions of RPh decreased constantly, from 180 in RPh I, to 48 species – RPh X. The information included in the herbal drugs individual monographs refers to the following requirements: *Title* in Latin (the first word is genus (genitive) and/or species (genitive) name, followed by the name of the organ used (nominative and singular) and Romanian name, *Synonims*, the *Definition* with the complete scientific name of the plant, the minimum content of quantified constituents (wherever possible). *Description* is according to the macroscopic and microscopic characters (also for pulverized herbal drug), being followed by the compartments: *Identification, Loss on drying, Total ash, Ash insoluble in 10% HCl, Dosage, Storage conditions, Pharmacological action and uses* (table) [19, 20, 21].

Certainly, quality normative documents, especially pharmacopoeial monographs, are intended to induce clarity in the standardization process,

and are the basis of safety in the use of herbal drugs, so that people can fully take advantage of the beneficial actions of medicinal plants, without any risks and dangers. To mention, that in the Republic of Moldova, the regulation of the quality of herbal drugs is mandatory according to the standards set out in the Ph. Eur. 10.0, according to the Order of the Ministry of Health of the Republic of Moldova Nr. OMSMPS no. 1490/2019 from 27.12.2019 [22].

CONCLUSIONS

1. The increasing use of herbal drugs and herbal medicines worldwide and the rapid expansion of the global market for these products, require safety and quality measures of medicinal plant materials that have become a major concern for health authorities, pharmaceutical industries, and the public.
2. Regulation and registration of herbal medicines varies from country to country. The analyzed pharmacopoeias (Ph. Eur. 10.0, USP 2022, the 14th Edition of SPRF and the RPh X) contain important requirements pertaining to certain analytical procedures and acceptance criteria that are relevant to herbal drugs.
3. Although the structure is not completely consistent between the analyzed herbal drugs pharmacopoeial monographs, investigating contents revealed approximately the same standardization requirements for herbal drugs, with some small exceptions:
   - The title of the herbal drug is indicated in the respective language and in Latin in all pharmacopoeias, while in the USP – only in English; the title is in the singular form in all pharmacopoeias, but in the SPRF it is written in the plural form.
   - The quantitative content is most often determined by modern chromatographic methods in USP (HPLC, HPLTC, GC) and Ph. Eur. Spectrophotometric methods are described most often in Ph. Eur., SPRF and RPh. We mention, that for identification, TLC is most often specified in all pharmacopoeias.
   - General monographs for each type of herbal drug are included only in the SPRF; also, the microscopic analysis is a very detailed one and includes many images that illustrate the respective micrographs.

- The pharmacological action and uses of the herbal drugs are specified only in the RPh.

Acknowledgments: *This study was supported by the Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova through the scientific research under the Moldovan State Program (2020-2023): "Complex research for the development of new local anti-infective pharmaceuticals for optimizing the pharmacotherapy of dental, oropharyngeal and auricular diseases" (nr. 20.80009.8007.14).*

BIBLIOGRAPHY

1. WHO (World Health Organization). WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues. WHO, Geneva 2007, ISBN 978 92 4 159444 8
2. Kunle F.O., Egharevba O.H., Ahmadu, & Ochogu, P. Standardization of herbal medicines - A review. International Journal of Biodiversity and Conservation, 4. 2012, 101-112.
3. "The European Pharmacopoeia," 10th ed. (Ph. Eur. 10.0), European Directorate for the Quality of Medicines, Strasbourg, 2021.
4. Choudhary N., Bhupinder S.S. An overview of advances in the standardization of herbal drugs. J Pharm Educ Res Vol. 2, Issue No. 2, December 2011.
5. WHO (World Health Organization). Quality control methods for herbal materials. WHO, Geneva 2011, 173 p.
6. Nandakumara S., Upton R., Rose U. et al. Pharmacopeial Standards for the Quality Control of Botanical Dietary Supplements in the United States, Journal of Dietary Supplements. 2021. DOI: 10.1080/19390211.2021.1990171
7. CDER/USFDA. Guidance for Industry, Botanical Drug Products, draft guidance, Center for Drug Evaluation and Research/U.S. Food and Drug Administration, 2000.
8. Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products, London, 2006. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-specifications-test-procedures-acceptance-criteria-herbal-substances-herbal-preparations/traditional-herbal-medicinal-products-revision-1_en.pdf (accessed 15.03.23)
9. Protocols on safety, efficacy, standardization, and documentation of herbal medicine (Iupac Technical Report), Pure Appl. Chem., Vol. 80, No. 10, pp. 2195–2230, 2008. doi:10.1351/pac200880102195

10. ICDRA. International Conference on Drug Regulatory Authorities, World Health Organization, 1986.
11. European Scientific Cooperative on Phytotherapy. https://escop.com (accessed 10.03.23)
12. WHO (World Health Organization). Regulatory situation of herbal medicines: a worldwide review. WHO/TRM/, Geneva 1998, 45 p.
13. WHO (World Health Organization). WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems. WHO, Geneva 2004, 18 p.
14. Good pharmacopoeial practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016.
15. Purusotam B. Promising Pharmaceuticals, IntechOpen, Croatia, 2012, ISBN 978-953-51-0631-9.
16. "The United States Pharmacopeia and The National Formulary," 2022 (USP-NF2022), United States Pharmacopeial Convention, Rockville, MD, 2022.
17. Shikov A.N., Narkevich I.A., Flisyuk E.V. et al. Medicinal plants from the 14th edition of the Russian Pharmacopoeia, recent updates. J Ethnopharmacol. 2021 Mar 25;268:113685. doi: 10.1016/j.jep.2020.113685. Epub 2020 Dec 11. PMID: 33309919.
18. Государственная фармакопея РФ XIV изд. Том Номер. ОФС. Номер «Название». [Электронное издание]. Режим доступа: http://femb.ru/femb/pharmacopea.php.
19. Farmacopeea Română, București, Ed. Medicală, 1993,1315 p.
20. Soroceanu V. Farmacopeea Română de la prima la ultima ediție, 150 de ani de la prima Farmacopee Română. Ed. Sitech, 2012, 202 p.
21. Benedec D., Oniga I., Hanganu D. Medicinal herbs in Romanian pharmacopoeias - 155 years of history, Hop and Medicinal Plants, Year XXV, No. 1-2, 2017 ISSN 2360 – 0179 print, ISSN 2360 – 0187 electronic, 69-78.
22. Order Nr. OMSMPS 1490/2019 of the Ministry of Health of The Republic of Moldova https://amdm.gov.md/storage/pages/September2021/7.Ordinul_MSMPS__Nr._OMSMPS_1490_2019_din_27_12_2019.pdf (accessed 25.03.23)