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10.2478/AMB-2023-0034

REVIEW

PHARMACEUTICAL REGULATION OF HERBAL MEDICINAL PRODUCTS IN THE COUNTRIES OF THE EUROPEAN UNION, THE USA, CANADA AND JAPAN

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Abstract. *The regulation of herbal medicines is changing and alters in the different countries. The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines medicines on the grounds of their intended use. Medicines shall be preliminarily approved by the FDA prior to their placing on the market or if they are OTC – they shall meet the requirements of specific regulations, called monographs, for their category. The definition of medicine according to the Canadian Food and Drugs Act (R.S.C., 1985, c. F-27) is "any substance or a combination of substances manufactured, sold or made available for use". In Japan, the objective of the Medicines and Medical Products Act is to improve public health by means of regulations that are necessary to guarantee the quality, the efficiency and the safety of medicines, quasi-drugs, cosmetics, medical and medicinal products. The definition of a medicinal product in the EU has been specified in Section I Definitions of Directive 83/2001/EC. In the aforementioned countries under consideration, medicines are classified into: medicines prescribed by a doctor (POM) and medicines sold without a doctor's prescription (OTC). The conducted comparative analysis of the aforementioned countries has shown that there are specific requirements and regulations for herbal medicinal products in the European Union. In the USA and Canada, herbal medicinal products are regarded as a subsection of the Federal Food, Drug, and Cosmetic Act (FD&C Act), sec. 351-360n-1 U.S.C. 379e; the Food and Drugs Act (R.S.C., 1985, c. F-27) – Government of Canada. In the Japanese legislation, there are no specific requirements for herbal medicinal products.*

Key words: *pharmaceutical legislation, herbal medicinal product, regulation*

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Received: *2 December 2022;* ***Accepted:*** *22 December 2022*

INTRODUCTION

The legislation and regulation of herbal medicines is changing and is different in the different countries. The reasons for this could be mostly related to the cultural aspects and also to the fact that herbal medicines are rarely the subject of scientific studies.

The issues related to plant-based medicines were first examined at the International Conference of the

World Health Organization (WHO) for regulation of medicines in 1986. WHO has published guidelines in order to establish the main criteria for the assessment of the quality, the safety and the efficiency of herbal medicines aimed at supporting the national regulatory authorities, scientific organizations and producers [1].

At present, almost all pharmacopeias in the world [2, 3, 4] contain herbal medicines with an actual medicinal value and in countries like Russia and Germany, there are separate pharmacopeias for plants. The monographs were written as official government documents to inform consumers and to facilitate the manufacturers' applications to register herbs as licensed drugs [5, 6].

The plant-based medicine is a medicinal product, the activity of which is determined by the content of the plant substance (drug) or after the processing of the plant substance (chopped, drug powder or extract). At present, the extraction of bioactive compounds and the synthesis of their analogues is an effective approach for developing plant products. The study of these compounds can result in obtaining valuable pharmaceutical, medical and other commercially important materials [7].

Purpose. The aim of the study is to present the specific nature of the legislative environment regulating the permission to use and disseminate herbal medicinal products in the EU countries, the USA, Canada and Japan.

MATERIALS AND METHODS

A comparative legislative analysis – this method has been applied when comparing the legislative requirements concerning the use and the dissemination of herbal medicinal products in the EU countries, the USA, Canada and Japan.

The analysis has been applied to the following normative documents:

- Directive 2001/83/EC for the establishment of a Community code relating to medicinal products for human use;
- Directive 2004/24/EC of the European Parliament and of the Council dated 31st March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use with reference to the traditional herbal medicinal products;
- Federal Food, Drug, and Cosmetic Act (FD&C Act), sec. 351-360 n-1 U.S.C. 379e;
- Food and Drugs Act (R.S.C., 1985, c. F-27) – Government of Canada;
- Japanese Pharmaceutical Affairs Law, Tokyo, Japan, Ministry of Health, Labour and Welfare.

RESULTS

As a result of our study, we have established that in the studied countries, the legislative requirements in the sphere of medicinal products are similar (Table 1). Thus, for example, in the examined countries, the requirements for medicines are strictly classified and stipulated in laws and directives. We have also established that for each country, there is a definition for a medicinal product in the legislation. With reference to the categories of medicines, there are two categories specified in the legislative documents: medicines prescribed by a doctor (POM) and medicines sold without a doctor's prescription (OTC). The requirements and the procedures applied to herbal medicinal products are similar to those registered as a medicinal product.

DISCUSSION

Owing to the need to specify and standardize the products of plant origin, the European Parliament has adopted Directive 2004/24/EU, which has introduced the term "conventional herbal medicinal products" and has established new rules for the registration of these products. As part of the execution of the Directive and Regulation (EU) 726/2004, a Committee on Herbal Medicinal Products was established in September 2004 at the European Medicines Agency. The Committee on Herbal Medicinal Products has the competence to prepare summarized monographies on the various medicinal plants and a list of the herbal substances, preparations and combinations intended for use, such as traditional herbal medicines [8].

The legislative environment in the studied countries has a number of requirements for pharmacovigilance. Pharmacovigilance is a science covering the activities related to the discovery, the assessment, the study and the prophylaxis of unwanted medical reactions or other problems related to medicines [9].

In the USA, in accordance with the legislative requirements, the FDS Adverse Event Reporting System has a program for post-marketing safety surveillance. It is a computerized information database consisting of reports on unwanted reactions caused by approved medicines and therapeutic biological products which FDA has received from producers in accordance with their regulation.

In Canada, the Canada Vigilance Program is a post-marketing surveillance system of Health Canada. The program was launched in 1965 for the purpose of collect-

Table 1. Main points from a conducted comparative analysis of the legislative framework concerning herbal medicinal products

	EU	USA	Canada	Japan
Regulatory authority/institution	European Medicines Agency (EMA), European Parliament, European Commission, Council of Europe	Food and Drug Agency (U.S. FDA) with U.S. Department of Health and Human Services	Health Canada – special office Food and Drugs Act Liaison Office	Ministry of Health, Labor and Welfare; Pharmaceutical and Medical Devices Agency
Medicines Act	Directive 2001/83/EC; Directive 2012/26/EU; Regulation № 726/2004; Regulation (EC) № 1223/2009	Federal Food, Drug, and Cosmetic Act (FD&C Act)	Food and Drugs Act; Regulations; Consumer Packaging and Labelling Act	Pharmaceutical and Medical Devices Act (PMD Act)
Product categories	– Medicines; – Medical products	– Medicines; – Medical products	– Medicines prescribed by a doctor (POM); – Medicines without a doctor's prescription (OTC); – Natural health products; – Medical products	– Medicines; – Quasi-drugs – Medical products – Class A to D
Definition of a medicine	A medicinal product is: a) any substance or a combination of substances said to have properties for treatment or prophylaxis of human diseases; or b) any substance or a combination of substances that can be used or prescribed to people for the purpose of restoring, rectifying or changing their physiological functions by performing a pharmacological, immunological or metabolic action or for the purpose of making a medical diagnosis.	FD&C Act defines medicines on the grounds of their intended use as: a "medicine" is used to denote (A) products recognized in the official Pharmacopeia of the USA, the official Homeopathic Pharmacopeia of the USA or the official National form or a supplement to any of them; and (B) products intended to be used for diagnosis, treatment, treatment or prophylaxis of diseases among humans or animals; and (C) products (other than food) intended to affect the structure or the function of the body of humans or other animals; and (D) products intended to be used as a component of each product specified in item (A), (B) or (C).	Food and Drugs Act (R.S.C., 1985, c. F-27) – Government of Canada – a medicine is "any substance or a combination of substances produced, sold or intended to be used: a) for diagnosis, treatment, relief or prevention of a disease, a disorder or an abnormal physical condition or its symptoms among people and animals; b) for recovery, rectification or modification of organ functions of people or animals' c) for disinfection of the premises where food is produced, prepared or stored.	The term "medicine" refers to the following substances: ● Substances registered in the Japanese Pharmacopeia; ● Substances (other than quasi-drugs) including dental materials, medical drugs and sanitary materials intended to be used for diagnosis, treatment or prevention of a disease among people or animals, which are not tools or equipment; ● Substances (other than cosmetics and quasi-drugs) which are intended to affect the structure or the functions of the body of people or animals, which are not tools or equipment.
Categories of medicines	– Medicines prescribed by a doctor (POM); – Medicines without a doctor's prescription (OTC);	– Medicines prescribed by a doctor (POM); – Medicines without a doctor's prescription (OTC)	– Medicines prescribed by a doctor (POM); – Medicines without a doctor's prescription (OTC)	– Medicines prescribed by a doctor (POM); – Medicines without a doctor's prescription (OTC)
Pharmacovigilance	Committee for assessment of the pharmacovigilance risk	FDA Adverse Event Reporting System; MedWatch	Canada Vigilance Program; MedEffect Canada – website	ICH MedDRA
Obligations for pharmacovigilance	Health specialists and producers – compulsory Consumers – voluntary	Health specialists and consumers – voluntary	Health specialists and consumers – voluntary Producers – compulsory.	Health specialists and producers – compulsory

ing and establishing reports on suspected side effects of the health products. The use of modern information and communication technologies worldwide will create significant advantages for more efficient use of resources and management of pharmaceutical care [10].

CONCLUSION

The conducted comparative legislative analysis in the studied countries has shown that there are specific requirements and regulations of herbal medicinal products in the EU countries. The role of the European Medicines Agency is to prepare, through its Herbal Medicinal Products Committee, scientific statements on the quality, the safety and the efficiency of such medicines so that the regulatory information related to them will be conformed with the frameworks of the entire European Union.

With reference to the USA and Canada, herbal medicinal products are regarded as a subsection of the Federal Food, Drug, and Cosmetic Act (FD&C Act), sec. 351-360n-1 U.S.C. 379e; Food and Drugs Act (R.S.C., 1985, c. F-27) – Government of Canada.

In the Japanese legislation there are no specific requirements for herbal medicinal products.

Disclosure Summary: *The authors have nothing to disclose.*

REFERENCES

1. World Health Organization. WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues. Geneva 27, Switzerland, 2007. https://apps.who.int/iris/handle/10665/43510
2. Council of Europe (COE) – European Directorate for the Quality of Medicines. European Pharmacopoeia 6th Edition. Strasburg, 2007.
3. British Pharmacopoeia Commission. British pharmacopoeia 2011. London: Stationery Office, 2011.
4. United States Pharmacopeial Convention. Council of Experts. The United States pharmacopeia: the national formulary. 31st revision, Washington, 2008.
5. Turcasso NM, Cooper JC. Herbal Medicine: Reliable Information Resources. Journal of Pharmacy Practice. 1999; 12(3): 187-195. https://doi.org/10.1177/089719009901200306
6. Nathan M, Robert S. The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines. Ann Intern Med. 1999; 130(5): 459 https://doi.org/10.7326/0003-4819-130-5-199903020-00024
7. Ahmed E, Arshad M, Khan MZ et al. Secondary metabolites and their multidimensional prospective in plant life. Journal of Pharmacognosy and Phytochemistry. 2017; 6(2): 205-214.
8. European Medicines Agency, „www.emea.europa.eu," 11 January 2007. [Online]. Available: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedure-preparation-community-monographs-traditional-herbal-medicinal-products_en.pdf. [Accessed 2022].
9. Valchanova V, Petkova VB, Pharmacovigillance and cosmetovigilance to the European legislatio. Science Pharmacology. 2014; 2: 4-8.
10. Kilova K, Mihaylova A, Peikova L. Opportunities of information communication technologies for providing pharmaceutical care in the COVID-19 pandemic. Pharmacia. 2021; 68(1): 9-14. https://doi.org/10.3897/pharmacia.68.e56987