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REGULATORY ASPECTS OF THE CONTROL OF DIETARY SUPPLEMENTS IN THE REPUBLIC OF SERBIA

ABSTRACT: The modern way of life often involves supplementing the diet with dietary supplements. By using them, we introduce additional vitamins, minerals, probiotics, and other substances with nutritional or physiological effects. These supplements are applied in dosage forms, and their safe use requires consistent adherence to regulatory requirements. Aspects of the control of dietary products include guidelines for production conditions, as well as physico-chemical and microbiological testing. Due to the specificity and widespread use of these products, the analysis requirements for product registration, as well as for product controls during the registration period, should be detailed, but also described in a way that enables their practical implementation. Regulatory aspects of statutory and mandatory requirements often differ in Europe, the USA, China, etc. This paper discusses the requirements of domestic regulations and proposals for their additions or corrections.

Keywords*: dietary supplements, regulatory aspects.*

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1. Introduction

In recent decades, there has been a noticeable trend of increasing use of dietary supplements. For this group of pharmaceutical products, according to domestic regulations, the terms food supplements and dietary supplements are used, and according to the Rulebook on Food Supplements, they are defined as: food supplements (dietary supplements), food that supplements the usual diet and that represents concentrated sources of nutrients or other ingredients with a nutritional or physiological effect, individually or in combination, and are sold in dosage forms such as capsules, pastilles, tablets, powder bags, liquid ampoules, dropper bottles, and other similar forms of liquid and powder intended for ingestion in small, dosed amounts (Rulebook on Food Supplements, 2024). The complexity of this definition points to the basic role of this group of pharmaceutical products, which is a dietary supplement, that is why it is important to look at the umbrella document in Serbia that deals with food: the Law on Food Safety (2019). The use of dietary supplements is associated with a healthy lifestyle and on the other hand, economic factors, such as higher incomes, a higher level of health insurance, and a higher level of education, are significant predictors of the frequency of dietary supplements (Baralić, Đorđević & Milinković, 2019; Satia-Abouta, et al., 2003). Also, the use of supplements in old age is becoming more and more widespread (Gariballa, Forster, Walters & Powers, 2006; Mahdavi-Roshan M., et al., 2021).

2. Requirements for conditions of production of dietary supplements

Dietary supplements as a category of pharmaceutical dosed forms must be produced under strictly defined production conditions, under the supervision of qualified employees, and with the use of defined active and auxiliary substances. Only under completely defined conditions and with compliance with the requirements for production conditions, the manufacturer can produce this category of products, which over time, according to regulatory requirements, is increasingly approaching the requirements for the production of medicines (Binns, Lee & Lee, 2018; Puvača, Vapa Tankosić, Ignjatijević, Carić & Prodanović, 2022).

Only when he provides the prescribed conditions can a manufacturer obtain a production license from the competent authorities. In our country, the production of nutritional supplements is under the supervision of the sanitary

inspection of the Ministry of Health. The conditions for this permit are: the application of regulations that prescribe production conditions, the Good Manufacturing Practice (GMP) Guidelines, which are also binding for drug manufacturers, the application of the HACCP principle and the ISO 22000 standard, which are among the mandatory conditions for food production, and are issued by certified bodies for evaluation and supervision of the quality management system (Vapa Tankosić, Puvača, Giannenas, Tufarelli & Ignjatijević, 2022).

The conditions for the production of dietary supplements are described in the Rulebook on sanitary and hygienic conditions for facilities where the production and trade of foodstuffs and general use items are carried out (1997) and the hygiene criteria in the Rulebook on general and special conditions of food hygiene at any stage of production, processing and circulation (2010).

3. Stages of registration of dietary supplements in the Republic of Serbia

The necessary conditions for the registration of dietary supplements are (reference):

1. precisely defined product composition (qualitative and quantitative),
2. product specification (basic features of the product and corresponding criteria by which steam production and quality control are monitored),
3. quality control analyses,
4. description of the production process with control points,
5. method of packaging and declaration.

Documentation on all the mentioned stages and product samples is the subject of further activities to approve the product for marketing.

For the placement of dietary supplements, i.e. for the permission of the Ministry of Health and the entry of a dietary supplement into the database of registered products, it is necessary to fulfill the requirements of the following three stages:

Phase I – expert opinion and categorization, with the approval of the text of the declaration by scientific institutions; for this step are authorized: Faculty of Pharmacy, University of Belgrade or Faculty of Pharmacy, Novi Sad.

Phase II – expert opinion and analytical report of the health institution on the health suitability of the dietary product; the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut", the Institute for Public Health of

Vojvodina, the Institute for Public Health Niš, the Institute for Public Health Kragujevac, the City Institute for Public Health Belgrade or the Institute for Hygiene of the Military Medical Academy in Belgrade are responsible for this type of report.

Phase III is the registration of the dietary product in the database of the Ministry of Health of the Republic of Serbia – the notification number is required in the text of the product declaration.

Regulatory procedures are different in different countries, but the framework covering production and product quality is similar worldwide (Binns, Lee & Lee, 2018). In Serbia, procedures are carried out following our laws and regulations, but with the full inclusion of EU guidelines. They define the quality of products and materials for their production, declaration, and quality control. When the same product is registered in several countries, documentation is prepared that is almost the same everywhere, and the declaration is adapted to local regulations, following what the regulatory bodies of that country have prescribed as the mandatory content of the text on the box and instructions for use.

4. Regulatory frameworks for dietary supplements in Europe

In Europe, the general principles and requirements related to food production are based on conclusions about the confirmed safety of food components in documents updated by the European Food Safety Authority (EFSA) and in the EU General Food Law EU General Food Law (2002) (Regulation (EC) No. 178/2002) (Vettoraz, Lopez de Cerain, Sanz Serrano, Gil, Azqueta, 2020). Other important EU documents in this sense are Directive 2002/46/EC, health and nutritional declarations Reg. EC 1924/2006, declaration Reg. EC 1169/2011, gluten regulation EU No 828/2024, food safety Reg EC 2073/2005, contaminants Reg EC 1881/2006, a single list of substances that can be added EC 1925/200, new food EC 2015/2283 and others.

The regulatory framework for dietary supplements in the Republic of Serbia is generally harmonized with the regulations of the European Community.

A large number of EU requirements have already been incorporated into local regulations, but the specifics of the conditions of production and markets, which in reality still do not formally belong to the EU, should also be considered.

5. Possible directions and proposals for supplementing the regulatory framework for dietary supplements in Serbia

The umbrella document, the Food Safety Low, and by-laws define the conditions for the production and control of dietary supplements. In this sense, the up-to-date Rulebook on establishing the Food Safety Monitoring Program for 2024, which defined the obligations of the competent ministry in terms of sample analysis to determine the level of contaminants, collecting data for risk analysis and checking valid standards, is also significant. This document, as well as other related documents, do not draw enough attention to nutritional supplements containing probiotic microorganisms, which are often intended for children up to 3 years of age. Given that the application of these products is expanding and the number of applied probiotic cultures is expanding, it is necessary to define the conditions for controlling the type of probiotics (EFSA database of approved probiotic strains) and the number of probiotic cells in the products during registration and the product expiration date (EFSA – European Food Safety Authority, EU General Food Law (Regulation (EC) No. 178/2002).

By looking at domestic regulatory requirements and requirements of pharmaceutical production, quality control, many years of experience in pharmaceutical production, and the aspects of preserving the health of the population, the authors of this paper draw attention to proposals for improving local regulations:

1. Since these are pharmaceutical-dosed products that exhibit unwanted effects, but also have contraindications as well as medicine, it is necessary to perform both qualitative and quantitative analysis after each produced batch. This proposal aims to fully control all manufactured batches (rather than the regulatory requirement to inspect one batch per year) and is a major step forward in terms of the safety of the use of dietary supplements on the market.
2. As dietary supplements are very often used as a supplement to drug therapy and as there must be products on the market that will improve people's lives, the product must contain the amount of active substance until the end of its use, and that is why it is important to add a stability test to the mandatory requirements. This requirement also contributes to the safety of the use of dietary supplements with the aim of controlled application of an effective, efficient, and safe product during the declared term and not only with data analysis at the time of registration and/or extension of product registration (Binns, Lee & Lee, 2018).

3. Improve the requirements that must be met by the production facility, related to the level of air cleanliness. With this request, we contribute to the aspects of the production of a safe product, primarily in terms of reducing contamination from the air during production.
4. Define the qualifications for the responsible person for the production of dietary supplements in the Rulebook. The requirement to define the responsibility of production is close to the requirements of drug production, but the justification for this position is the fact that dietary supplements are dosage pharmaceutical forms with significant application in prevention and therapy and deserve a serious approach and definition of production responsibility.
5. Multidisciplinary approach to define specific requirements in the phase of product registration: analysis of probiotic supplements (confirmation of the name of the probiotic strain, monitoring of the number of probiotic cells, etc.). We are witnessing an increasing number of probiotic products on the market, and the laboratories that test these products at the time of registration often do not have a methodology for determining the number of probiotic cells that compares their activity (Zavišić, Ristić, Petković, Šaponja, 2023). The recommendation is a more detailed approach to the regulatory framework for the production, control, and declaration of probiotics following the IPA Europe International Probiotic Association and with the experiences of countries that have already done so (Denmark, France, Italy, etc.) (IPA, 2024).
6. Requests for more detailed analyses during the registration period (larger number of microbiological and physico-chemical analyses than currently required – supplement analyses of the content of selected heavy metals – mandatory determination of cadmium content). The control of the content of heavy metals in the product is of great importance from the aspect of product safety and the increasingly present cumulative effect of the presence of heavy metals in food and water (Zavišić, et al., 2023).

The above proposals are certainly guidelines for more detailed control of dietary supplements, and from the point of view of increasing production costs, they represent an additional burden on domestic producers, but from the point of view of protecting the health of the population, they represent a significant contribution. Also, by adopting the recommendations for improving the regulatory requirements, we are getting closer to the requirements of production and business conditions in the EU.

5. Conclusion

In recent decades, dietary products have proven many positive effects on health and have become an integral part of modern life. Therefore, regulatory effects are very significant because they are directly related to safe and effective application. The authors of this paper propose suggestions for national regulations: qualitative and quantitative analysis after each produced batch, add a stability test to the mandatory requirements, level of air cleanliness in production area, define the qualifications for the responsible person for the production of dietary supplements, detailed analysis of probiotic supplements and generally detailed analyses during the registration period.

The adoption of recommendations for the improvement of national regulations would contribute to the quality of dietary products and greater confidence in their benefits.

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REGULATORNI ASPEKTI KONTROLE DIJETETSKIH SUPLEMENATA U REPUBLICI SRBIJI

APSTRAKT: Savremeni način života često podrazumeva dopunu ishrane primenom dijetetskih suplemenata. Njihovom primenom unosimo dodatne vitamine, minerale, probiotike i druge supstance sa hranljivim ili fiziološkim efektom. Primenjuju se u doziranim oblicima i za njihovu bezbednu upotrebu neophodna je dosledna primena regulatornih zahteva. Aspekti kontrole dijetetskih proizvoda podrazumevaju uputstva za uslove proizvodnje, fizičko-hemijska i mikrobiološka ispitivanja. Zbog

specifičnosti i široke rasprostranjenosti primene ovih proizvoda zahtevi analiza za registraciju proizvoda kao i za kontrole proizvoda tokom perioda registracije treba da budu detaljni, ali i opisani na način koji omogućuje njihovu praktičnu primenu. Regulatorni aspekti propisanih i obaveznih zahteva često se razlikuju u Evropi, SAD, Kini i dr. U ovom radu razmatrani su zahtevi domaće regulative i predlozi za njihove dopune ili korekcije.

***Ključne reči**: dijetetski suplementi, regulatorni aspekti.*

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