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Review of Regulatory Requirements for the Safety Monitoring of Food Supplements and OTC Medicines, Containing Caffeine and/or Taurine Extracts Derived from Plants

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Abstract: Globally there is an increasing popularity and constantly growing use of dietary and food supplements, energy drinks and medicines containing Caffeine and/or Taurine herbal extracts. The problems of the existing pharmacovigilance system are associated with the specifications of plant products and food additives: their different regulatory status in the country of origin and the different requirements for them; complex and heterogeneous in chemical composition; problems with the classification and identification of the botanical origin of the plants; tendency of growing number of patients who use treatment with herbal products and consume energy drinks; very low rate of reporting of side effects and adverse reactions. Among the challenges for the system of safety monitoring of medicines and food supplements containing plant extracts are solving the problems associated with the nomenclature used in herbal substances, ensuring quality and control; issues related to consumers; issues related to the identification of side effects and adverse reactions. The growing use of energy drinks and Caffeine containing products will inevitably lead to the need for brief and strictly regulated monitoring methodology for safety surveillance of plant products and risk reducing measures, regardless of their status as medicinal products or food supplements.

Keywords: Pharmacovigilance, Food Supplements, Caffeine, Taurine, Drug Safety

1. Introduction

Globally there is an increasing popularity and constantly growing use of herbal products that can be either in the form of dietary and food supplements and medicines with or without a prescription, or energy drinks. More and more cases of side effects and adverse reactions are associated with the use of such products, and this raises the question of their safety.

Currently in Bulgaria there are more than 30 different brands of energy drinks, both locally produced and imported 12 over-the-counter (OTC) medicines and varying number of food supplements, containing Caffeine and Taurine. The annual consumption of energy drinks in Bulgaria reached about 11 million liters or an average of 1.5 liters per capita.[14,15] According to the last legal requirements it is obligatory for products, containing higher doses of caffeine to be marked with a warning label on the package, that the drink contains more than 150 mg of caffeine/liter.[1,11,12] This is a way of prevention, which warns that these drinks should be avoided by pregnant and breastfeeding women, children, and patients suffering from diabetes and hypertension. Drinks on the basis of mineral water with caffeine as a substitute of morning coffee dose are getting more and more popular on the European market.[13]

Energy drinks increase physical and mental activity, the ability to focus, accelerate the pulse. In most cases those effects are due to the content of extracts from plants such as Guarana – a natural source of caffeine, Kava Kava, Ginseng, Ginger, etc. Some of the marketed energy drinks contain

extracts of Cranberry, Cat's claw, Cordyceps. It is typical for most of the producers to reach the high ingredient of caffeine by including extracts from Green tea, combined with Yerba mate, Ginkgo biloba, Passiflora, Aloe vera, Echinacea. Hence, safety monitoring of products containing Caffeine and/or Taurine plant extracts, including energy drinks, food supplements and medicines without medical prescription is essential for the health of consumers. [14]

The existing system of pharmacovigilance of synthetic chemical and biological medicines should be extended in a way that allows enhanced safety monitoring of herbal products and food supplements. Their inclusion in the existing system becomes increasingly important and very necessary on the basis of their increased consumption. Herbal products are often used in combination with other medicines and it is extremely important to understand the possible consequences of such combinations. Since these interactions have a high potential to cause side effects it is vital to provide an effective safety surveillance system.

According to the Bulgarian Food Law "Dietary supplements are foods, which supplement the normal diet and which are concentrated sources of vitamins and minerals or other substances with a nutritional or physiological effect, used alone or in combination, and which are marketed in dosage forms such as capsules, tablets, powder, liquid ampoules and other similar liquid or powdered forms, intended to be administered in a pre-dosed small quantities.[1]

There are no strict regulatory requirements for food supplements as these for medicinal products. They do not undergo clinical trials either. [20] Food additives are subject only to a notification procedure and there is not a legislative requirement for producers to obtain a specific authorization after a long approval process. Acting laws in Bulgaria do not provide requirements for quality control of food supplements (such as Good Manufacturing Practice for medicines) [2] and/or obligatory system for safety monitoring.[19]

There are only specific demands concerning the provision of information to the public by labeling or by an advertisement. In the EU the general requirements for provision of information, advertising and labeling of food and food additives is regulated by Directive 2000/13/EC. The Directive prohibits the use of information that would mislead the consumer and would prescribe medicinal properties of food. In the EU there are stringent requirements for health claims made on food. [17]

The existing system of pharmacovigilance has been developed specifically for medicines with synthetic chemical, biological and blood origin and it should be modified to meet the specific characteristics of the medicinal plants. Although such modifications are necessary, many authors do not recommend the development of two separate systems, as this would lead to confusion and reduced rate of reporting. The World Health Organization /WHO/ takes a step in this direction and develops guidelines, which describe the specific challenges facing the system for the safety monitoring of herbal medicinal products and proposes some measures to address them, egg "WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems".[3]

2. Objective

The study aims to investigate the current methods and good practices for pharmacovigilance of OTC medicines and food supplements, with ingredient of Caffeine and/or Taurine containing herbal extracts. We plan to analyze the legislative requirements, current problems and future challenges for safety monitoring of herbal products.

3. Methods

A literature review of good pharmacovigilance practices for herbal medicines in Bulgaria, Europe and the US and a systematic review of current legislation requirements for collection, systematization and analysis of data collected for adverse reactions of OTC medicines and side effects of food supplements, containing Caffeine and/or Taurine herbal extracts were performed. Bulgarian Food Safety Agency database search could not be conducted because of rejection to our request for access to the non-public Register of food supplements, marketed in Bulgaria. [7]

4. Results and Discussion

4.1. Challenges in Safety Monitoring of Herbal Products

The deficiency of the existing system of safety monitoring of Caffeine/Taurine containing energy drinks and food supplements is a result of the specific characteristics of herbal products, namely their different regulatory status in the countries of origin, complex and heterogeneous chemically composition, difficulties with the nomenclature and identification of botanical origin of the plants, tendency of self-healing, very low rates of reporting of side effects. A problem worth mentioning is the unexpected toxicity of plant products as a result of lack of effective quality control process – poor quality of the plant material, misidentified plant, improper processing, and contamination of the raw material.

4.2. Methods for Monitoring the Safety of Herbal Medicines

Classical pharmacovigilance methods can be applied to safety monitoring of herbal products but they need to be modified to meet the specific requirements related to the characteristics of this new branch of vigilance system.

There are two main methods for post marketing safety monitoring: 1) spontaneous reporting of adverse reactions and 2) conducting non-interventional studies. It should be clarified that those methods are relevant when herbal products have the status of medicinal products.

4.3. System for Spontaneous Reporting of Adverse Reactions

"Spontaneous report is a report about a suspected adverse reaction to a medicinal product voluntarily sent to the marketing authorization holder or to the responsible

authorities or other organizations, which is not derived from a research or another organized system for gathering information." To be valid the spontaneous report must contain 4 obligatory elements: 1) suspected product; 2) adverse reaction/event; 3) patient (subject to an ADR/event) and 4) author of the report (for feedback).

There are several examples of functioning systems for spontaneous reporting: In the US, where herbal products have the status of dietary supplements, medical professionals and consumers may report suspected adverse events to MedWatch system (The FDA Safety Information and Adverse Event Reporting Program). In the UK system for reporting ADRs is known as a "yellow card". In 2000 the "yellow card" has been modified so that it can be used for reporting adverse reactions of herbal products. The UK Medicines and Healthcare Products Regulatory Agency receives around 20,000 yellow cards annually. About 100 of the mentioned reports are related to the use of products, containing herbal extracts. Spontaneous reports are more effective when herbal products have the status of medicines and the healthcare professionals are well educated about their obligation to report adverse reactions. Since many years there is a unified system for spontaneous reporting of ADRs for The EU - EudraVigilance. The regulatory agencies and the marketing authorization holders from all EU member states can send reports to EudraVigilance directly.[17]

4.4. Sources of Information in the ADR Spontaneous Reporting System

There are three main sources of spontaneous reports. The first one, which is considered to be the most reliable is the group of healthcare providers, who are obliged to report to the marketing authorization holder and/or to The Bulgarian Drug Agency any suspected serious or unexpected adverse reactions. The second source of information is the scientific literature: medical journals, guidelines, publications describing clinical case studies. Patients and consumers are the third main source of adverse event reports. Since July 2012 patients of all member states of the EU are able to report suspected adverse reactions directly to the authorities.[16]

4.5. Regulation of Safety Monitoring of Herbal Products

The legislative requirements for herbal products safety monitoring in Bulgaria are provided by five main sources:

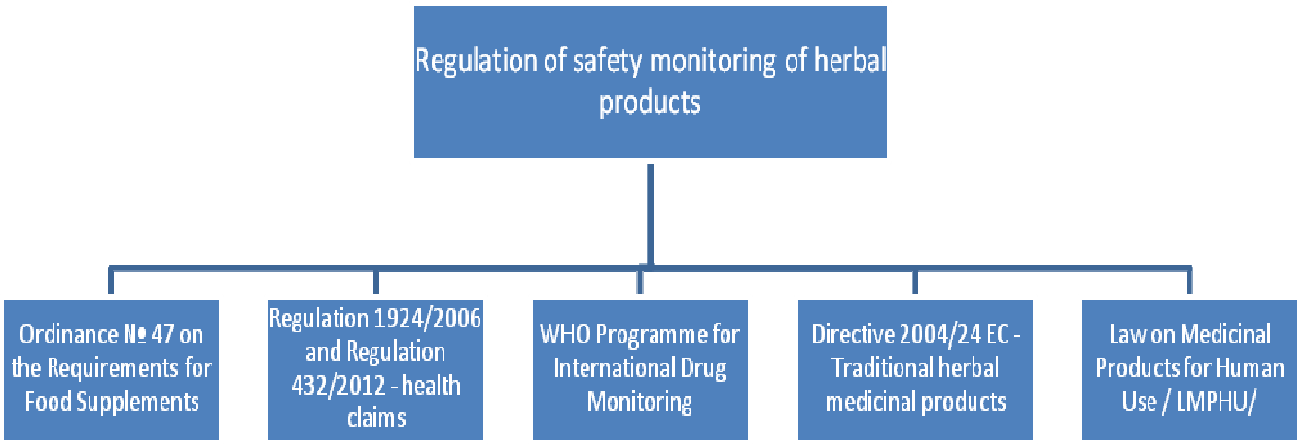

Figure 1. *Regulation of safety monitoring of medicines and food supplements, containing plant extracts*

4.5.1. Ordinance № 47 on the Requirements for Food Supplements

The majority of Caffeine/Taurine containing herbal products in Bulgaria has the status of dietary or food supplements and they are not required to pass through a marketing authorization procedure. Manufacturers or traders who launch a dietary supplement into Bulgarian market shall notify the Regional Directorate of the Bulgarian Food Safety Agency /BFSA/ by submitting a notification form and attaching a draft model of the label which will be used on the package. The BFSA develops and maintains a non-public database of the submitted notifications of the marketed food supplements.[1]

If it is established as a result of new information or reassessment of the existing data that a food supplement, which complies with the requirements for being marketed, threatens the health of consumers, a package of corrective actions can be applied. The measures include temporary and permanent withdrawal or suspension from the market, prohibition of the use of the food supplement, definition of special conditions of use or marketing of the supplement; or other appropriate measures depending on the situation. According to the Bulgarian Food Act competent authorities inform immediately other Member States of the European Union and the European Commission of the measures taken and send a brief explanation of the reasons for these actions.[1]

4.5.2. Regulation 1924/2006 and Regulation 432/2012 - Health Claims

According to Regulation (EC) 1924/2006 of the European

Parliament and of the Council on nutrition and health claims made on foods in commercial communications, the use of health claims made on foods are prohibited unless they are authorized by the Commission in accordance with that Regulation and they are included in the list of permitted claims. According to the Regulation, the use of a health claim for a specific product within the Community must be scientifically evaluated by the European Food Safety Authority. The use of a health claim is permitted only after a detailed product characterization is composed and it is proved that the food additive meets it. Health claims use cannot be authorized unless they are based on valid scientific evidence and in accordance with generally accepted nutrition and health principles.

Health claims for dietary supplements are not permitted if: suggest that consumption of the product may affect health; claims are referring to the reduction of weight, or to the recommendations of individual doctors, other health professionals or healthcare associations.

Health claims made in relation to food products, containing Caffeine and/or Taurine can be authorized after submitting an application to the competent authorities of a Member State. Within the context of this authorization procedure, submission of brief review of scientific research and results, proving the health claim is required. If necessary, the applicant may be obliged to provide additional information.

Claims for disease risk reduction and claims relating to the children health and development can be authorized if they have been previously published in the list of approved claims and after an application submission. In this case, the label or advertisements of dietary supplements must contain information about the impact of multiple risk factors on the disease.

Manufacturers, who intend to use health claims, not published in the list can apply for inclusion of the specific claim.

The Commission shall maintain a public register of nutrition and health claims made on foods that contain all authorized claims, specific conditions of use and a list of rejected health claims and the reasons for their rejection.[5,7]

4.5.3. WHO Programme for International Drug Monitoring

Since 1970 The World Health Organization has always had a serious influence on the pharmacovigilance process. The *WHO Collaborating Centre for International Drug Monitoring* defines the basic principles of safety monitoring policies, while *Uppsala Monitoring Centre, (UMC), Sweden is responsible for their practical implementation.* The program currently includes a network of 70 national independent pharmacovigilance centers, whose functions are coordinated and supported by WHO and the UMC. The monitoring center in Uppsala maintains the global database of WHO (VigiBase), which contains all adverse event reports sent by the national pharmacovigilance centers. That database is used to identify/detect a signal from the data collected and for risk assessment procedures, conducted by the UMC. The aim is to rule out the possibility to omit specific adverse events because of the low rate of reporting in each of the countries. To date VigiBase contains more than 3 million reports of suspected adverse reactions.[6]

4.5.4. Directive 2004/24/EC – Traditional Herbal Medicinal Products

The European Medicine Agency defines the purpose of the Directive: "to remove the differences which create obstacles to the free movement of medicinal products in the European Union, while ensuring protection for public health". The directive provides two simplified procedures for launching herbal medicinal products into the European market on the basis of evidence on their safety and efficacy.

4.5.5. Law on Medicinal Products for Human Use /LMPHU/

The law provides the legislative framework for herbal products, which have the status of medicines with or without a medical prescription in Bulgaria.

According to the Act the Bulgarian Drug Agency /BDA/ is obliged to organize and maintain a system for safety monitoring of marketed medicines. The agency shall forward electronically all the submitted data about a suspected adverse reaction to the European Medicines Agency, regulatory authorities of the member states and the marketing authorization holder within 15 days.[7]

The law decrees that the marketing authorization holder also shall develop a safety monitoring system and employ a qualified person for pharmacovigilance /QPPV/ in the territory of a Member State, who is responsible for reporting any collected data about serious or/and unexpected adverse reactions from Bulgaria or another member state within 15 days.[7] The legal entity that holds the marketing authorization is obliged to submit periodic safety update reports /PSURs/ to the BDA that provide an evaluation of the impact of the reports on the risk-benefit balance of the medicinal product.[7]

4.6. Regulatory Measures for Safety Concerns of Herbal Medicinal Products

On the basis of a signal risk assessment competent authorities conduct the most appropriate corrective action. Measures may include the following:

1) Requirement for the marketing authorization holder to conduct further research to gain more evidence about the safety concern;

2) Changes in the product information, such as reducing the dose or editing/correction of indications and contraindications;

3) Temporary withdrawal from the market;

4) Suspension of the marketing authorization. In these cases EMA and competent authorities of the Member States must be notified within one working day.

Medical professionals, patients and the public are informed about the corrective measures by different ways of communication depending on the character and the emergency of the signal. These feeds include web publications; information provided to patient organizations and professional

organizations of health care specialists; information provided by the media, as well as direct communication to healthcare professionals.[9]

5. Conclusion

The existing pharmacovigilance system should be revised and updated with the provision of additional safety monitoring and surveillance procedures regarding to dietary and food supplements, OTC medicines and energy drinks with plant extracts, containing Caffeine and/or Taurine. The general tendency to optimize and extend the scope of pharmacovigilance regulation does not exclude dietary supplements and foods with health claims. The growing use of energy drinks and Caffeine containing products will inevitably lead to the need for brief and strictly regulated monitoring methodology for safety surveillance of plant products and risk reducing measures, regardless of their status as medicinal products or food supplements

References

[1] Ordinance № 47 of 28 December 2004 on the requirements for food additives.

[2] Aronson, J., Edwards, R., Adverse drug reactions: definitions, diagnosis, and management. The Lancet, October 2000, Vol. 356.

[3] Shaw, D., et al. Pharmacovigilance of herbal medicine. // Journal of Ethnopharmacology, 2012, N140, c. 513-518. (May 2012)

[4] Regulation 1924/2006 of the European Parliament and of the Council on nutrition and health claims made on foods.

[5] Regulation 432/2012 - establishing a list of permitted health claims made on food, other than those referring to the reduction of disease risk and children's development and health.

[6] Shetti, S., et al. Pharmacovigilance of herbal medicines: Current state and future directions. *Pharmacognozy Magazine*, 2011, N 25, pages 69-73.

[7] Law on Medicinal Products for Human Use, published 2007

[8] Directive 2001/20 / EC of the European Parliament and of the Council of 4 April 2001. 2012. <http://ec.europa.eu/health/files/eudralex/...2001_20/dir_2001_20_bg.pdf>

[9] Directive 2004/24 / EC of the European Parliament and of the Council of 31 March 2004. 2012. <http://ec.europa.eu/health/files/eudralex/...2004_24/dir_2004_24_bg.pdf>

[10] Calixto, J.B., et al. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). *Brazilian Journal of Medical and Biological Research,* 2000, N2, pages; 179-189.

[11] Ordinance on the labeling and presentation of foods of 29.07.2001, updated 2014.

[12] Regulation (EU) № 1169/2011 of the European Parliament and of the Council of October 25, 2011 on the provision of food information to consumers.

[13] Opinion on Caffeine, Taurine and D-Glucurono - g -Lactone as constituents of so-called "energy" drinks (expressed on 21 January 1999)-http://ec.europa.eu/food/fs/sc/scf/out22_en.html

[14] Opinion of the Association of Manufacturers of Soft Drinks in Bulgaria on the benefits of energy drinks-http://www.bsda-bg.org/index.php?ul=5.

[15] Petrova, St., Duleva, V, Health risks associated with high consumption of energy drinks. Regulation of energy drinks-http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=482&categoryid=3670&articleid=3705.

[16] Directive 2010/84/EU of The European Parliament and of the Council of 15 December 2010 amending, as regardless pharmacovigilance, Directive 2001/83 EC. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf.

[17] Ditova, M, Grigorov, E., et al, Review of regulatory requirements for the safety monitoring of medicines and dietary supplements derived from plants.Social medicine. Mart 2013, Vol. 21, No. 4, p. 39-42.

[18] Kostov, E., Belcheva, V., Grigorov, E., Drug regulation – history, present and future. Proceedings of the 13th national scientific session, Pleven, Bulgaria, Octomber 2014, Vol. 8, No.2, p. 112-129.

[19] Grigorov, E., et al. Food Supplements – marketing and health claims analysis, *Archives of the Balkan Medical Union,* 2011, Vol. 46, No. 4, Suppl.1, p.26-29.

[20] Kostov, E., Grigorov, E., Belcheva, V., Hristova, P., Review of the historical aspects in the development of clinical trials. Asklepios, December 2013, Vol. 8, No.2, p. 39-46.