Legal trade of food supplements

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The characteristics of food supplements

Specific category of foodstuffs

- concentrated sources of nutrients and others substances with nutritional or physiological effect
- supplement the normal diet
- marketed in dose form
- authorized health claims: support normal functions of the body, reduction of disease risks, development and health of children

Law and Regulations

- **EU horizontal rules** applicable to foods in general
- **EU specific rules** applicable to food supplements
- **National specific rules** of Member States in the absence of relevant EU rules

BOTANICALS

Considering certain botanicals under particular use, Member states have a long tradition of regulating botanicals, imposing requirements onto domestic producers to follow these rules but also aiming to protect their markets against products not complying originating from other Member states or non-UE countries.

Relevant legislation applicable to food supplements

- Regulation (EC) no. 178/2002 (General Food Law)
- Directive 2002/46/EC (Food Supplements)
- Regulation (EC) no. 1925/2006 (Addition of other substances)
- Regulation (EC) no.1924/2006 (Claims)
- Regulation (EC) no. 258/1997 (Novel Foods)
- Regulation (EC) no. 1169/2011 (Food Information for consumers)

How a food supplement enter the market

- Food business operators must notify national authorities when a food supplements is first placed on the market;
- In certain Member States prior marketing approval is necessary, in other countries the notification is done latest on the day when the product was placed on the market;
- There are also countries where notification is not compulsory (Austria).
- Notification has to be sent to the competent authority: Ministry of Health (Italy, Slovenia, Croatia, UK), Ministry of Food, Agriculture and Fisheries (Denmark), Ministry of Agriculture, Food Production and Legislation Department (Czech Republic), National Institute for Food and Nutrition Science (Hungary, Romania), Food Safety Agency (Finland, Bulgaria), Federal Office of Consumer Protection and Food Safety (Germany), National Food and Veterinary Risk Assessment Institute (Lithuania), Chief Sanitary Inspectorate (Poland), General Directorate for Competition Policy, Consumer Affairs and Fraud Control (France), Federal Public Service-Health, Food Chain Safety and Environment (Belgium);
- Online notification is also practiced, in Poland or Belgium, respectively, where FOODSUP digital notification system was implemented since 2012.

Notification procedure

- The notification and registration procedures could be more or less different as approach, but the criteria of food safety evaluation are similar in European countries.

- According to Directive 2002/46/EC, a particular reference to composition (ingredients and levels) and compliance to European regulation regarding food safety, novel food ingredients, food additives and specific requirements for labelling, nutrition and health claims have to be taken into account

Safety assessment of food supplements

Safety assessment (public health and nutrition point of view) and risk management measures are based on the examination of data provided by the food business operator:

- ✓ type and amounts of active ingredients
- ✓ chemical forms of minerals and vitamins
- ✓ recommended daily dose
- ✓ plant species and their parts used
- ✓ conditions of use of botanicals
- ✓ botanical preparation (drug or plant extract: ratio, active substance, maximum levels)
- ✓ specific warning statements, etc.

Positive and negative lists of botanicals

- Positive lists of non harmonised botanicals (plant species and their parts that can be used in food supplements) are regulated under national legislation and are common in many countries, such as: Italy, Hungary, Germany, Belgium, France, Check Republic, and Romania. Botanical Advisory Boards or Expert Committees which members are coming from the universities, academy of sciences, research institutes of food and nutrition, professional associations, ministries, etc. are responsible in each country for evaluation of botanicals and other active substances intended for use in food supplements.
- There are also negative lists (in: Sweden, Netherlands, Lithuania, Bulgaria, and Netherlands) as well as restricted botanicals (maximum levels), which are used as national guidance in the absence of a harmonised list on EU level.

Specific reason for worry in botanicals

- Some of the secondary metabolites of safety concern are: the alkaloids (especially pyrrolizidin content), anthraquinones, coumarins and furanocoumarins. They could have hepatotoxic, genotoxic, neurotoxic, carcinogen, and mutagen, drastic emetic, laxative or abortive effects
- In connection with the scientific progress and new discoveries, negative lists as well as conditions of use are revised continually
- Derogation possibility and exemptions to the prohibition have to be supported by toxicological studies and analytical tests that prove the final product is free of toxic properties and do not contain the toxic substances synthesized by the plant used as raw material
- EU harmonisation for botanicals in food supplements is still a goal to achieve because there is a common interest to have on the European market safe products with plausible physiological effects. Harmonisation is possible when coherent policies based on scientific advice and pragmatic approach is implemented, taking traditional use into account and assure safety and consumer information

Notification dossier

- All characteristics of the product should be evaluated technical and scientific point of view. The food business operators must prepare the notification dossier and supply the competent authority with details about the product: technical specifications, list of ingredients (plant name, part used, galenic form, amount, % active substances, function), preparation/processing method (% solvent, Drug-Extract-Ratio), quality and safety test reports (chemical and biological contaminants) labelling (nutritional analysis, qualitative and quantitative data of nutrients, health claims), additional information for imported food supplements, etc.
- The competent authority has to check all information provided by food business operator as well as product conformity with vertical and horizontal legislation. Usually there are registered: rewording of the label, need for more specific information, expert advice when necessary, certain recommendation, etc.

Helpful claim legislation in borderline issues

- To ensure a high but proportional level of consumer protection and information it is also important to respect always precautionary principle for daily recommended dose, to inform specific target group and to label the product with safety warnings.
- Borderline issues and distinction between food and medicine products have to be based on case-by-case risk assessment, available scientific data, EMA and WHO monographs.
- If necessary, for “ambivalent” plants the maximum level (% of minimal daily therapeutic dose obtained after evaluation of clinical trials for well defined indication) have to be taken into account.
- The claims legislation should be helpful in establishing the status of the product (traditional herbal medicine product versus herbal food supplement) but in case of botanicals a huge number of health claims were not yet evaluated or are still on hold.

Herbal food supplements market

- The EU market of botanical food supplements (retail-direct sales-internet) was estimated to 2, 1 billion euro. Actually 75% of the sales are registered in France, UK, Italy, and Germany, which are considered the biggest markets.
- The herbal food supplement markets are really dynamic: thousands of new products are notified each year, for example 3,000 in Belgium or 4,500 in Italy. Since 2006 up to 2015, a number of 25,000 products were notified in France, 20,000 in Italy, and 16,000 in Hungary.
- As compared to food supplements, traditional herbal medicine products market is considerably smaller: since 2004 about 1,300 applications were granted EU wide, covering 150 plant species. It could be noticed that 77% of applications were submitted in only 6 countries

Distribution channels and legal trade

- Markets are different from a Member State to another. Herbalists, health care practitioners, pharmacies, groceries, supermarket/retail are involved in herbal food supplements distribution, protecting their market structure against sales of products through other channels.
- The direct sales as well as the online channels have become popular platforms for manufacturers in their efforts to reach a diverse and broad set of customers. Products are sold via online pharmacies, dedicated health platforms, retailers' and manufacturers' websites and not least via Amazon (one of the largest online retailers), which and are often offer significant discounts. Beyond easy price comparisons, the online channel also facilitates consumers' research of products' ingredients and benefits prior to purchase.
- Retailers have taken note that internet is often the first port of call when in need of information on health and have focused efforts on improving the online shopping experience through better online education and targeted marketing. Online pharmacies are required by German law, for example, to provide the option of personal advice via telephone or email and some websites now have live chat options to help instantly address specific consumer questions. Such methods have increased consumers' comfort level for buying dietary supplements online.

Herbal products' control and market surveillance

- It is underlined the fragmented legislation between the Member states, the difficulty to overview and control all players in the sector.
- A real problem seems to be to make enforcement actions respected (there are actors that close down and restart again, as well as websites which are moved abroad).
- Unfortunately the lack of nutravigilence, few unscrupulous importers/ producers responsible for most of the issues, the difficulty to police the internet as well as illegal products (often advertised and sold via internet) give the impression of an unregulated market, while some gaps in the legislation create feeling of lack of control.
- Even if the vast majority of botanicals is not disputed (safety and quality concerns focus on a limited number of species), the EU legislation is not so well equipped to address the specificity of botanicals, while the national approaches are too focused on consolidating historic situations.

Difficulty of herbal food supplements control

- EFSA is emphasizing the difficulty of herbal food supplements control due to the enormous diversity of products.

- The huge number of plant species and their combination, different matrices (solid, liquid) and forms of presentation, methods of preparation (from traditional to modern and sophisticated techniques) are listed as serious issues

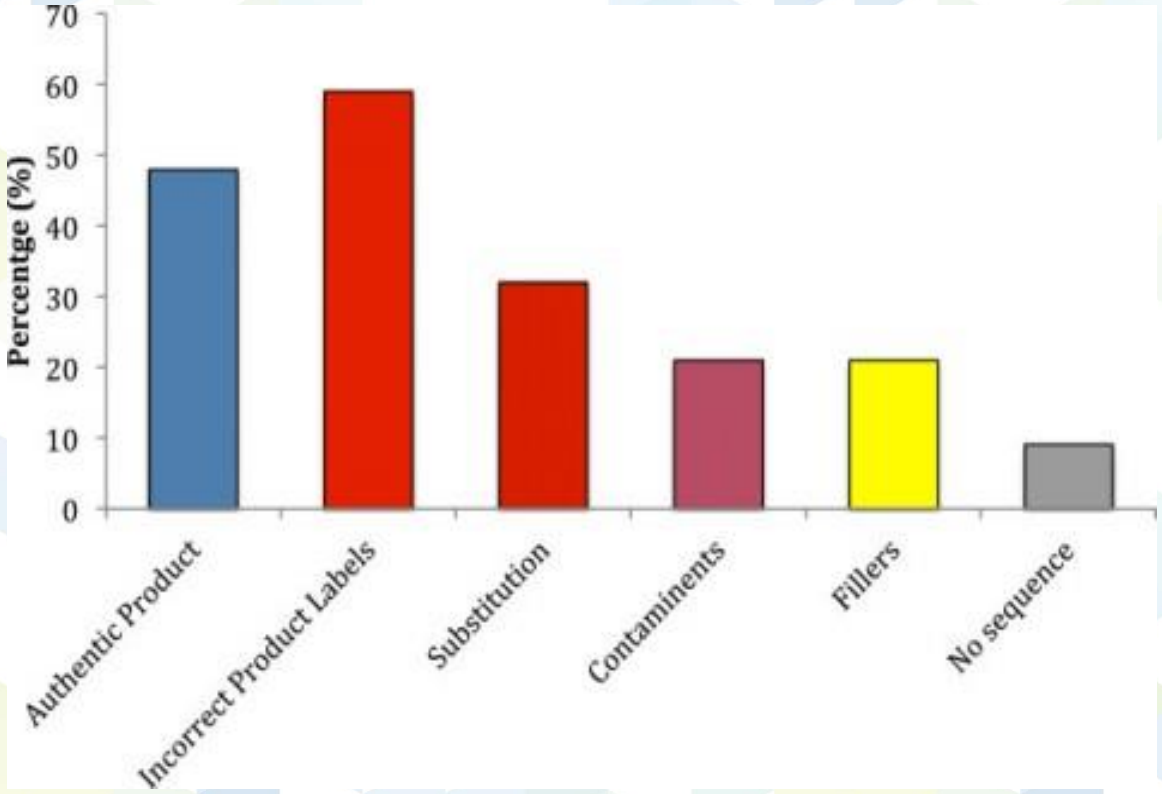
- competent authorities are involved not only in raw material quality and safety control, but also in food supplements fabrication process, which is more severe controlled.

- All ingredients and products must comply with the general regulations regarding foodstuff, as well as with the specific regulation regarding food supplements .

Main risks and health threats of illegal trade

- The control authorities are faced during the last period to an increasing phenomenon which affect both the governments (financial point of view), and the population/food supplements consumers (health point of view).
- The phenomenon is called “herbal food supplement fraud” and has been characterized as the “deliberate and intentional substitution, addition, tampering or misrepresentation of food, food ingredients or food packaging, false or misleading statements made about a product for economic gain”
- This intentional act can lead to adverse public health consequences, such as “counterfeit, poor quality or food adulteration”, which are, according to WHO a real “threat to consumer safety”.
- Fortin (2011) assumed that adulteration of food supplements could be a potential “terrorist weapon” and a serious problem for the security of any country.

Product authenticity



Results of herbal food supplements authenticity analysis (Newmaster et al, 2013)

Adulteration

- Adulterations can be classified in:

✓ addition of orthodox drugs to herbal medicines,

✓ substitution (use of fake or inferior plant materials),

✓ addition of foreign materials (non-official/forbidden herb parts, sand, metals) (Zou et al., 2006).

- food supplements are suitable vehicles for adulteration with drug substances. In most countries food supplements are loosely regulated compared to medicines. Consumers buying place a high trust in natural remedies and probably are less likely to attribute adverse effects to the product.
- The most frequent intentional adulterated food supplements are those categories of products for which the market demand is increasing: body-building, slimming, sexual performance enhancers, anti-diabetic or fatigue relief products.

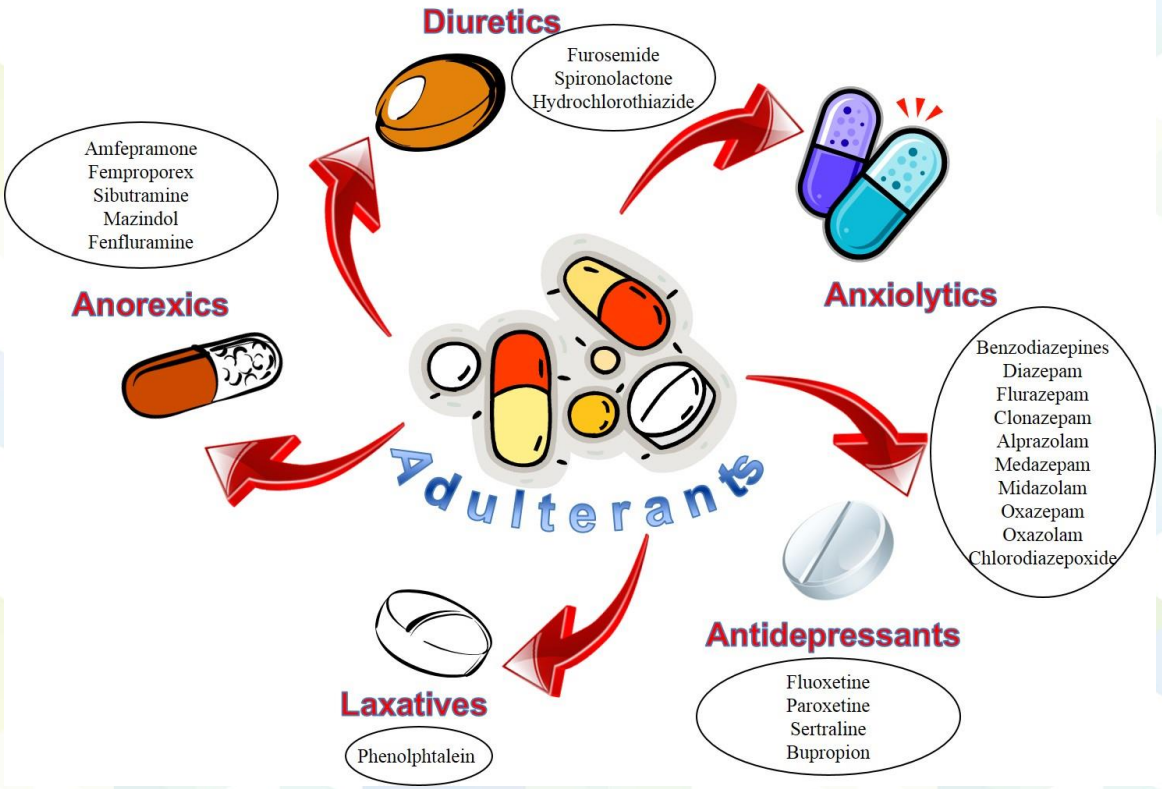
Sexual performance enhancers

- Many dietary supplements advertised as all natural, have in contrast been found to contain synthetic PDE-5 inhibitors; these commercially available herbal products have been spiked with legal drugs or mainly their analogues, which have not been subjected to formal pharmacokinetic or other pharmacological testing
- The discovery of PDE-5 inhibitors (sildenafil, tadalafil and vardenafil) revolutionised the management of erectil disfunction and oral drug therapy -independent of the disorder etiology- is currently the first therapy option. These drugs are only available with prescription and must be used under medical control.
- PDE-5 inhibitors are not recommended for patients who ingest medicines based on organic nitrates (e.g. nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, amyl nitrite, or nitrate) for diabetes treatment, hypertension, hyperlipidemia and ischemic heart disease, because may result in marked and unpredictable decreases in blood pressure, accompanied by symptoms of hypotension.
- The adulteration of dietary supplements has become a major problem for both public health and control authorities because the number of PDE-5 inhibitors analogues grows rapidly (more than 50 adulterants were identified in 2013.
- The safety and toxicity profile of these unapproved analogues is often not known and hence consumers of such products are exposed to higher health risks, because their physiological effects are not sufficiently studied and supplements that contain such substances are not properly labelled.
- In order to detect these substances new analytical methods for rapid screening are needed to be developed as well as new strategies for structural elucidation of unknown analogues.

Slimming and weight management products

- Obesity has become one of the diseases of modern civilization, having a negative impact on quality of life and consequently on lifetime
- Effects of herbal food supplements, designed to reduce body weight are much slower as compared to synthetic drugs. In order to increase efficiency, weight loss supplements are commonly adulterated with pharmaceutically active substances such as sibutramine and its analogues, rimonabant, benzodiazepine, fluoxetine, furosemide, phenolphthalein, etc.
- Sibutramine was approved in 1997 by FDA as a drug for treating obesity (manufactured by Abbott's Meridia). Due to side effects it was withdrawn by EMA in January 2010, and in September, 2010 by the FDA.
- A quantity of 2-5 times higher than in Reductil® or Meridia® authorized drugs was find in slimming capsules.
- in food supplements for the management of body weight were also detected a number of six analogues of sibutramine.
- In other studies, there were detected dietary supplements adulterated with: N-nitrozofenfluramine, fenfluramine, propanolol, dobutamine, rimonabant, efedrine, norpseudoefedrine (natural compound of *Catha edulis*), furosemide, orlistat, fentermine, clopamid, emodine, crisofanol şi reine (secondary metabolites of *Rheum rhabarbarum, which* induce diarhea and have a carcinogenic potential).

Pharmacological classes of adulterants found in dietary supplements for weight control

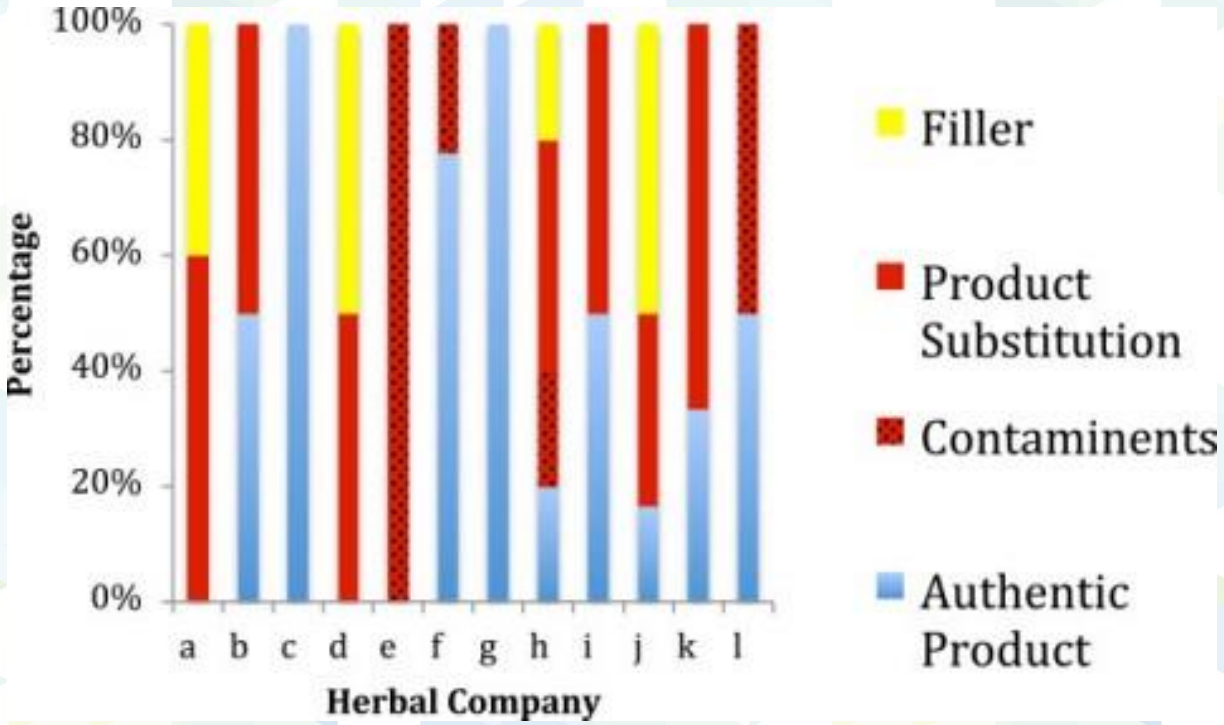


Carvalho et al., 2011

Substitution

- Currently best practices in place for identifying the various ingredients are used in herbal products
- This is because the diagnostic morphological features of the plants on which the current Linnaean taxonomic system is based cannot typically be assessed from powdered or otherwise processed biomaterials
- As a result, the marketplace is prone to contamination and possible product substitution, which dilute the effectiveness of otherwise useful remedies, lowering the perceived value of all related products because of a lack of consumer confidence in them.
- Some of the products were of such poor quality that harms could be expected
- One sample was labelled as containing St. John's worth (used to treat depression) but actually only contained senna, a laxative. Another product was contaminated with black walnut, which has a nasty side effect profile
- there's also the undisclosed wheat in some products, which would be harmful to those with Celiac disease or a wheat allergy
- Other studies have raised similar concerns: a study of 131 herbal teas revealed only 58% of products could be authenticated, and 33% were contaminated;
- half of the ginseng products examined in one study contained other forms of ginseng than the labelled *Panax ginseng*, etc.

Results of a screening of authenticity in herbal products



Results of authenticity analysis of 44 herbal products (samples provided by 12 companies-Newmaster et al., 2013)

Mislabelling

- The frequency of product mislabelling in herbal products became a safety problem and has been estimated at 14-33%
- Whilst the online market for dietary supplements is flourishing, different institutes for risk assessment and consumer protection agencies have been increasing their efforts to warn customers about its particular challenges
- With thousands of products available to buy online, not only from domestic, but also non-EU suppliers, customers are considered to be at increased risk from non-licensed ingredients, misleading advertising and missing health warnings
- Increasing public education about possible risks poses a minor threat to the development of the online market for health products, but at the same time represents a chance for trusted and established brands to shine.

Promotion and advertising of food supplements

- Misleading advertising (advertisements which mislead the consumer regarding:
  - ✓ scientifically not substantiated health claims;
  - ✓ low level of active ingredients which do not support the efficacy;
  - ✓lack of side effects of natural products
- Comparative advertising (advertisements which mislead the consumer but it is also detrimental to a competitor)
- Use of non-authorized claims in labelling or product promotion
- Induce voluntary consumer confusion (food supplements vs traditional herbal medicine products)

Present and future challenges for food supplements

EU harmonization

- Need for harmonization of other substances than vitamin and minerals, especially for botanical substances (borderline products: NAC, DHEA, glucosamine)
- Review of the safety of botanicals in a systematic way
- Evaluation of claims used for botanicals and botanical preparations in member states of EU (EC project 2015-2016)
- Notification of national rules is on the rise in absence of EU rules and create problems in implementing Regulation (CE) no. 764/2008 regarding mutual recognition (local manufacturers are discriminated)
- Positive list of botanicals (BELFRIT initiative; German compilation)
- Maximum level of vitamins and minerals