Perspective

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Assessment and management of new and emerging risks for Europe's dietary supplement companies operating with botanicals

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Abstract: This study identifies new and emerging risks in the botanicals sector with the aim of fostering the success of nutraceutical and dietary supplement companies based on quality, product safety, and consumer trust. Focusing on the Italian nutraceutical market, an analysis was conducted based on interviews with experts. The outcomes of the analysis and the resulting guidelines on how to manage safety and quality by preventing risk at firms commercializing botanical-based nutraceuticals and dietary supplements are of direct relevance to industry practitioners and to bioeconomy and biotechnology scholars. © 2020 Society of Industrial Chemistry and John Wiley & Sons Ltd

Supporting information may be found in the online version of this article.

Key words: nutraceuticals; botanicals; bioeconomy; dietary supplements; food guidelines

Introduction

Botanicals, plant-derived compounds, used as food supplements and nutraceutical ingredients form a rapidly growing sector of the bioeconomy, which is currently undergoing significant changes in terms of product specification and regulatory aspects.[1] Change has even accelerated in relation, for example, to the role of bioactive ingredients of foods and herbs for the support of the human immune system against infections such as COVID-19.[2] The sector is currently regulated as a sub-category of the dietary supplement sector, with no specific rules and directives, and no legal distinction between botanicals, vitamins, and minerals.

Legally identified as food companies, companies involved in the development, production, and distribution of nutraceuticals, dietary supplements, and functional foods in EU countries need to comply with legislation that regulates the food sector and that aims to ensure that only safe products are commercialized.[3,4]

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In the case of botanical products, problem arise from the fact that issues with the availability of raw materials often lead companies to purchase raw materials from foreign countries with different (and often loose) regulatory frameworks, and different contamination standards.[4]

In 2006, the World Health Organization launched the International Regulatory Cooperation for Herbal Medicines.[5] The aim was to promote public health and safety through improved regulations for herbal medicines, and in an effort to harmonize analytical methods, qualitative acceptance criteria, and contamination limits in raw and refined botanicals.

In Europe, all harmonized qualitative acceptance criteria, limits, and certified analytical techniques suitable for use in the analysis of botanicals are reported in Regulation 1881/2006/EC, which sets maximum levels for certain contaminants in foodstuffs,[6] and Regulation 396/2005/EC on maximum residue levels of pesticides in or on food and feed of plant and animal origin.[7] Unfortunately, neither of the regulations has been updated since its release. This lack of upgrading to new and more specific analytical protocols (technologies) in the subsequent 15 years can lead to analytical errors (around 15%), especially for complex matrices such as botanicals.[8]

Change also concerns the state-of-the art botanical ingredient production technologies applied in the field. It is enough, for example, to consider the technologies used today for recovery of biophenols from olive-mill wastewater,[9,10] or of grape biophenols from grape byproducts.[11]

In EU countries, food and food supplement companies willing to add nutrition and health claims to the labels of their products need to follow the requirements specified by Regulation 1924/2006/EC.[12] The regulation dictates the claims that may be used in communicating the product's nutrition and health attributes to customers. Marketing language or reinterpretation of the approved claims can lead to product withdrawal from the market for re-labeling, causing monetary, legal, and reputation costs to the company. Consumers, in turn, may interpret the withdrawal of non-compliant products as the outcome of poor product quality, losing interest in *all* products marketed by the company.

In general, botanical-based dietary supplements represent one of the main examples of regulatory fragmentation in the European single market due to the divergence in safety and efficacy product assessments as well as in marketing and communication rules. A recent evaluation of the Nutrition and Health Claims Regulation ('Claims Regulation') adopted in 2006, covering the period from 2005 until the end of 2015, concluded that 'in the current situation the objectives of the Claims Regulation are not fully attained. Furthermore, the current rules of the Claims Regulation do not take into account the specific situation of plants and/or their preparations, which have a long traditional history of use linked to health benefits.'[13]

With the aim of enabling nutraceutical and dietary supplement companies to succeed on the marketplace based on product quality, safety, and consumer trust, this study identifies new and emerging risks in the botanicals sector. Italy's nutraceutical market is Europe's largest in terms of production, consumption, and exports.[14] Furthermore, the country has one of the strictest regulatory frameworks for dietary supplements, including post-marketing supervision and label notification programs for almost all nutraceutical products marketed. Hence, focusing on the Italian nutraceutical market, the following analysis addresses four key aspects that are considered to be of global relevance: (i) product quality, (ii) product safety, (iii) relationship with suppliers and distributors, and (iv) product communication. Guidelines on how to manage safety and quality by preventing risk at small and medium enterprises commercializing botanical-based nutraceuticals conclude the study.

Results and discussion

The research methodology is described in detail in the supplementary information. In brief, besides the analysis of the available literature, expert interviews were conducted, which involved selecting eight experts through a non-probability sample technique (judgment sample technique) as a reliable source of accurate information.

Product quality and efficacy

All the interviewed executives agreed that there is now a requirement to ensure quality, safety, and efficacy of marketed products, and the introduction of quality assurance and quality control procedures for all production stages, from purchase and analysis of raw materials to production and shelf-life identification.

In any company, including nutraceutical companies, quality is achieved through the prevention of mistaken or incomplete processes.[15] Hence, operating procedures and instructions, and workforce training are generally used along with product analyses performed on a daily basis. Digital technology for product traceability, and certification of products and processes to the highest industry standards are equally important tools in the quality-management process (Fig. 1).

According to all the responders we surveyed, audits of suppliers are used systematically to evaluate whether buyers

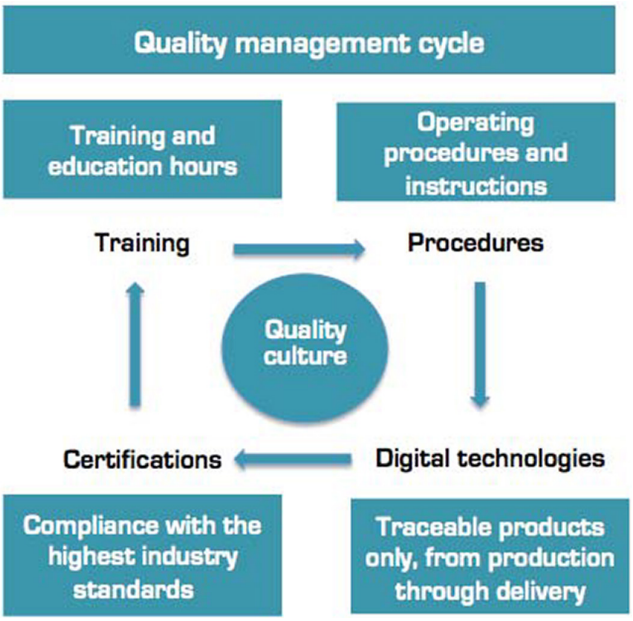

Figure 1. The quality management cycle includes, but is not limited to, quality control and quality assurance.

are respecting required quality limits (first step in external risk management). Food-grade declarations on raw materials are not constant around the world; thus, this certification has no legal meaning. Legal rights in use and marketing can be obtained only if the products respect limits established by the competent authorities of the country in which products are marketed.

Despite competent European national authorities advising all companies operating in botanicals to adopt internationally recognized quality standards, the adherence level to these principles is currently relatively low due to the increased operating costs.

Similarly, in Europe, there is no legal requirement to certify the producing plant because botanical firms are registered as food companies. Introducing mandatory good manufacturing practice (GMP) rules specific to the botanical sector could represent a first line of defense against most production risks.

Currently in European legislation there is no standardized or mutually accepted criteria regarding product efficacy. A botanical-based product that has never been tested for efficacy can be legally marketed.

According to Regulation 1924/2006/EC, even if a company possesses scientifically proven safety and efficacy information acquired from human intervention tests, this information cannot be communicated to the consumer or to medical doctors unless approved by the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition, and Allergies.

Product safety

The use of botanicals and botanical preparations as ingredients in food supplements in EU countries needs to comply with the existing EU food legislation, which includes maximum permissible levels of chemical and biological contaminants such as pesticides, mycotoxins, heavy metals, and foodborne pathogens, as well as techniques for ensuring quality, and the application of good hygienic practice, including hazard analysis and critical control point (HACCP) methodologies.

In 2009, the EFSA published a guidance document on safety assessment of botanicals and botanical preparations intended for use in food supplements.[16] In brief, botanicals or botanical preparations for which an adequate body of knowledge exists can benefit from a 'presumption of safety' without any need for further testing. To assist manufacturers and food safety national authorities by facilitating hazard identification, in April 2009 the same agency published on its website a compendium of botanicals that may be used in food, including supplements reported to contain toxic, addictive, psychotropic, or other substances of concern. A second version of the compendium was published in 2012,[17] and it is since regularly updated.[18]

The safety of other botanical ingredients should be assessed following analyses providing information on:[16]

- the method(s) of manufacture (e.g. the process by which the raw material is converted into a preparation, such as extraction or other procedure(s), and plant extract ratio);
- substances entering the manufacturing process, (e.g. the identity of the extraction solvent, reagents, special precautions including light and temperature);
- standardization criteria (e.g. see the European Pharmacopeia); and
- interaction of phytocomplexes comprising most botanical-based dietary supplements with other active molecules such as those contained in medicines.

This was shown by the recent cases of cholecystic hepatitis in curcumin consumers with hepatic dysfunction, which led Italy's Ministry of Health to update rules governing the use of plant preparations and extracts originating from the *Curcuma* genus. Now manufacturers need to label preparations containing curcuma with a warning label ('In the event of alterations of liver function, biliary or calculosis of the biliary tract, the use of the product is not recommended' and 'If you are taking other pharmaceutical treatments, it is appropriate to seek the advice of a physician'), applying to subjects with liver conditions.[19]

Similarly, bioavailability enhancers such as cytochrome P-450 inhibitors like piperine, or carrier inhibitors like turmeric oil, are often added to dietary supplements, introducing the hidden risk of overdose, because bio-enhancers may cause the uptake of a potentially unsafe dose. Similarly, when the bio-enhanced botanical is taken in association with a medicine, the unwanted alteration of the drug's active ingredient pharmacokinetics could result in hazardously high blood levels.

Relationship with suppliers and distributors

Enhanced communication with suppliers and distributors, namely the first and the last partners in the nutraceutical product value chain (Fig. 2), is critical in the pursuit of the production and commercialization of quality dietary supplements and nutraceuticals. Suppliers, buyers, and distributors share economic interests and common risks.

It is no longer possible to accept a raw material as safe and usable only on the basis of a product's certificate. Only traceable raw materials are acceptable, delivered with the outcomes of third-party analyses from accredited laboratories with reference to contamination limits complying with European regulations.

Sharing data and information should include a protocol for the early communication of hazards. Sharing information indeed substantially increases the ability to prevent risk and mitigates the consequences of any quality issues.

Early communication of a hazard chain can lead to mitigation of risk, while delay or absence in communication can lead to severe consequences.

Similarly, to reduce the transfer of risk between companies involved in the same value chain, and to mitigate the impact of possible production hazards, all the responders agreed that industrial partners should introduce and mutually share a procedure to produce proper written track records of daily operations.

Every action related to the batch product – production, pest control, raw materials purchasing, waste disposal, equipment maintenance, and analysis should be recorded in a simple and well-designed, way, using for example the Standard Operating Procedures (SOPs) format.

Product communication

All of the experts who were interviewed agreed that labeling and advertising are two of the most critical aspects for today's botanical-based dietary supplements and nutraceuticals. Current regulations dating back to 2011, in terms of which botanical products are labeled as food, vitamins, and mineral products,[20] were considered by the interviewed experts to be outdated for botanical products.

Figure 2. Nutraceutical product value chain.

For example, all approved health claims refer to a 'general healthy person in the absence of overt pathologies both chronic and acute.' However, this definition can no longer be accepted because about 32% of the European adult population suffers from hypertension, 20% suffers from osteoporosis, 35% is diabetic, and more than 90% of the population over 70 years old is affected by one or more chronic pathologies.[21]

The evaluation of safety and efficacy should be aimed not only at the healthy population but also at the significant share of it with a pre-pathological or pathological status, taking into account how the introduction of a xenobiotic agent (the botanical substance) will modify the homeostasis status of an individual.

Finally, the experts interviewed agreed that, in the near future, the information reported on the label of dietary supplements and nutraceutical products will be inserted following clinical trials whose outcomes are approved by the competent authorities.

Conclusions and recommendations

So far, producing and marketing a botanical dietary supplement in Europe has been relatively easy: companies do not need to undertake complete safety assessments and only have to notify the competent national authorities of the label and product composition.

The eight experts interviewed for this study, however, agreed with several scholars[22] and other industry practitioners[23] that a healthy and prosperous future for the industry requires better, stricter regulation of production, certification, and marketing practices.

According to a recent market analysis, the global food botanicals market was approximately $1186 billion in 2018 and is expected to generate around $1489 billion revenue by 2025, growing at 3.2% compound annual growth rate between 2019 and 2025. Based on application, the market is fragmented into beverages, supplements, confectionery, and flavor enhancers, with food supplements holding the largest market share in 2018. The size and relevance of the dietary supplements market suggest that a coherent set of rules is likely to evolve soon, both in the EU and in the rest of the world.

Four main guidelines emerge from this succinct study aimed at identifying and managing risks in small and

medium enterprises within this important sector of Europe's economy.

First, scientifically validated studies should be carried out to evaluate the safety and efficacy of existing and new products, not only on healthy subjects but also in a population with pre-pathological or pathological conditions, as well as with subjects who are consuming medicines or other xenobiotic products. Smaller companies that lack the internal skills or equity to perform these studies (the costs of which can approach €1 million) would partner with other companies in dedicated consortia also involving, for example, public research institutes.

Second, using an ethical and professional communication approach, companies are recommended to start the provision of scientifically sound information – for example by organizing seminars aimed at consumers, medical doctors, and pharmacists – to reduce the risk of incorrect prescriptions and the misuse of their products. Organized for example in collaboration with the nutraceutical company national association, these activities should be free from any advertising purpose and should rather be aimed at communicating the scientific rationale for high-quality botanical products.

Third, given the accelerated pace of innovation in the digital era, companies should continuously improve the content and the quality of educational activities aimed not only at shop-floor operators and researchers but also at middle and top management, to include improved management methodologies such as systems thinking and action learning, in which learning generated by work is captured and shared in a continuous process.[25]

Fourth, companies should establish tight and mutually beneficial relationships with all company partners in the value chain, from raw material suppliers to product distributors, based on continuously shared information. Today's digital information and communication technologies enable such data and information sharing at unprecedented levels and at an affordable cost.[26]

In conclusion, it is thanks to their products that nutraceutical companies using botanical ingredients will build their success in today's and tomorrow's marketplace. Inevitably, such excellence requires talented and well-educated people at all stages of the nutraceutical product value chain, from research and development, through to formulation, production, and distribution.

Contrary to old management beliefs, such enhanced quality levels are not achieved through enhanced 'command and control' but rather through enhanced workforce and management education, improved information sharing, and by a systems approach to the design and management of work,[25] adopting a systems view of work in which product and process innovation (including, of course, new botanical extraction technologies – for example from waste from the agrifood industry)[27] assume a central position.

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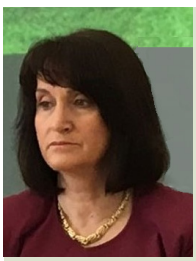

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