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Legislation relating to nutraceuticals in the European Union with a particular focus on botanical-sourced products

Om P. Gulati [a,*], Peter Berry Ottaway [b]

[a] *Scientific & Regulatory Affairs, Horphag Research Management SA, Avenue Louis-Casaï 71, 1216 Geneva, Switzerland*
[b] *Berry Ottaway & Associates Limited, Hereford, United Kingdom*

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Abstract

Nutraceuticals are food or food ingredients that have defined physiological effects. They do not easily fall into the legal categories of food or drug and often inhabit a grey area between the two. These products in general terms cover health promotion, "optimal nutrition" the concept of enhanced performance – both physically and mentally – and reduction of disease risk factors.

In this paper the focus is mainly on legislation governing botanical-sourced nutraceuticals in the European Union (EU). Nutraceutical concept in general has been defined. Different pieces of legislation influencing botanical nutraceuticals are described. The issue of the borderline between food and drug is discussed. The regulatory status of botanical nutraceuticals as food supplement, food ingredient, functional and fortified food, novel foods and foods for particular nutritional use in the diversified, complex and ever-changing European regulatory environment is described.

Botanical nutraceuticals present additional problems because of their complex nature and composition particularly with respect to the quality aspects, which in turn affect safety parameters and overall efficacy of the products. Quality issues relating to botanical sources, growth conditions, end products, their specifications and other technical criteria are highlighted. Guiding principles to be observed for conducting in vitro, in vivo studies in animals and their impact on clinical safety data are discussed.

Finally, health claims, their types and criteria of substantiation in light of ongoing discussions with regard to the EU frame work of regulation on nutrition and health claims and role of process for the assessment of scientific support for claims (PASSCLAIM) initiative is discussed. The concept of grading of evidence to substantiate different claims and to establish standards, which should not be revoked or reversed by emerging science at a later stage has been considered. These issues are crucial and are being discussed at EU Parliament and Commission level during the development of the health claim regulations.

Keywords: Food and nutraceutical regulations; European Union (EU) legislation; Health claims; Process for the assessment of scientific support for claims (PASSCLAIM); Foods for specified health use (FOSHU); Foods for particular nutritional use (PARNUTS)

1. Introduction

Nutraceuticals is a term coined to describe substances which are not traditionally recognized nutrients (e.g. vitamins and minerals) but which have positive physiological effects on the human body.

The term was originally used by Defelice in 1995 with the definition: "A food or parts of food that provide medical or health benefits, including the prevention and/or treatment of disease (Defelice, 1995)".

As they have defined physiological effects nutraceuticals do not easily fall into the legal categories of

* Corresponding author. Tel.: +41 22 710 2650; fax: +41 22 710 2600.
E-mail address: om@horphag.com (O.P. Gulati).

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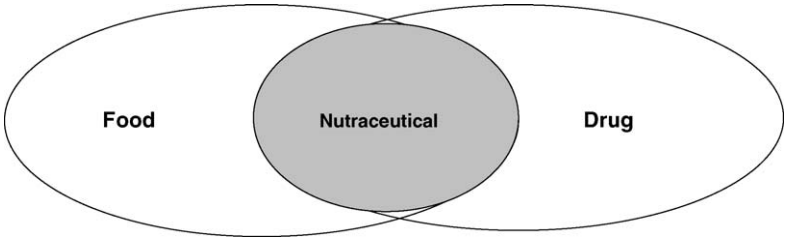

Fig. 1. Nutraceutical occupies position between food and drug.

food or drug but inhabit a grey area between the two (Fig. 1).

Within European Union (EU) law the legal categorization of a nutraceutical is, in general, made on the basis of its accepted effects on the body. Thus, if the substance contributes only to the maintenance of healthy tissues and organs it may be considered to be a food ingredient. If, however, it can be shown to have a modifying effect on one or more of the body's physiological processes, it is likely to be considered to be a medicinal substance.

The development of foods and food components that provide benefits beyond their traditional nutritional value has created tremendous academic, commercial, regulatory and public interest. These products in broad sense cover health promotion, "optimal nutrition" and concept of enhanced performance – both physically and mentally – and reduction of disease risk factors. They represent nutraceuticals, functional and fortified foods (Richardson, 1996). Broadly, functional and fortified foods are those with a similar appearance to their traditional counterparts, while nutraceuticals are components that are often consumed in unit dose forms such as tablets, capsules or liquids and commonly known as food/dietary supplements. The nutraceutical, functional and fortified food sectors have grown significantly in Europe during the last decade.

The challenges ahead relate to quality, safety and efficacy. In many cases there are still a number of unknowns such as the identification of specific active components, their absorption and metabolism in the human body and the effects of processing on the products containing them.

Botanical materials represent a large segment of nutraceuticals and present additional problems relating to the complex nature and composition of botanical ingredients. Botanicals in this context represent whole, fragmented or cut plants, algae, fungi, lichens and botanical preparations from these materials involving extraction, distillation, expression, fractionation, purification, concentration and fermentation. Botanical substances are defined by the botanical name of the plant according to the binomial system (genus, species, variety and author) and the part used (e.g. leaf, root and fruit).

In this chapter the focus will mainly be on legislation governing botanical-sourced nutraceuticals in the European Union.

Within Europe, the regulatory status of nutraceuticals is diversified due to differences in tradition, historical and cultural backgrounds and different legislation and enforcement practices at national level within the 25 member states.

2. Nutraceutical concept in European Union

Much of the early development of the nutraceutical concept and products was driven from the United States of America where, since its introduction in 1994, the Dietary Supplement and Health Education Act (DSHEA, 1994) has allowed considerable flexibility and blurred the boundaries between foods and medicines found in other parts of the world.

Under DSHEA a dietary supplement may contain 'an herb or other botanical' or 'a concentrate, metabolite, constituent, extract or combination of any ingredient from the other categories'. This is subject to very little qualification and as a consequence a wide variety of botanicals and other substances have been sold as dietary supplement ingredients, including many that are considered to be medicinal substances under most regulatory regimes in EU countries.

This liberalism in the interpretation has not been reflected within the EU. In 1998 a report on a study carried out on behalf of the European Commission by the AESGP, the European Association of the Self-Medication Industry concluded that several EU member states seemed to face problems in applying identical rules to all medicinal products in a uniform manner. The report which has the title 'Herbal Medicinal Products in the European Union' found that there was no consistency between the 15 member states in the interpretation of the medicines Directive 65/65/EEC with respect to herbs (AESGP, 1998). The criteria used to differentiate between medicinal and food herbs varied widely.

To further complicate the problem it was found that in terms of indications and efficacy there was also no agreement between the countries. For example, garlic (*Allium sativum*) is used for colds and coughs in the United Kingdom whereas in Germany it is sold for the prevention of arteriosclerosis. In the UK there are some garlic products licensed as medicines whilst in the same market there are a number of garlic products being sold as supplements under food law. In Germany the law prevents garlic being sold in unit dose form as supplements.

Within European Medicines law a nutraceutical can be defined as a medicine for two reasons:

1. if it presented for the prevention, treatment or cure of a condition or disease, or
2. if it can be administered with a view to restoring, correcting or modifying physiological functions in human beings.

Over the years the interpretation of the second part of the definition if a medicine has been based on the accepted function of the substance. Thus, a vitamin at levels around the daily requirement (Recommended Daily Allowance) is considered to maintain the function of healthy organs and tissues and is regarded as a food ingredient. However, if a substance can be demonstrated to modify the functions, or to restore or correct the functions, the substance or the product containing it may be considered medicinal.

When considering the original definition of a nutraceutical in terms of European law there is a high probability that many substances will fall into the classification of medicinal rather than as a food ingredient.

3. Regulatory frame work including regulatory status of botanicals in different EU countries

As already discussed there is currently no consistency in the legal status of some botanicals across the EU. In some EU countries, botanical products are sold as foods, or incorporated in functional/fortified foods or as food supplements, meaning that no medicinal claims are made, whereas in other EU countries these preparations are seen as herbal medicines registered by full or simplified registration procedures. In some countries, the medicinal product status is automatically linked to pharmacy-only status.

1. Although the definition of a medicine is given in EU legislation (Directive 2001/83/EC, formerly 65/65/EC) as amended by Directive 2004/27/EC, it has been interpreted differently by member states in the context of products containing botanicals.

   The definition is in two parts and a product falling into the scope of either part is considered a medicinal product under law.

   The first part of the definition relates to the presentation of the product and any statements or implications that the product can prevent treat or cure a human condition or disease can make the product medicinal. Under EU food law it is illegal for a food product to make such expressed or implied statements (i.e. prevention, treatment or cure).

   The second part relates to the function of one or more components in the product. The text in the legislation states, “Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medicinal diagnosis” can be a medicinal product. Thus, if any of the components have a pharmacological effect on the human body the product can be considered medicinal, even though no ‘medicinal’ statements are made in its labelling or presentation. A product falling into the scope of the second part is described as being ‘medicinal by function’.

   It is the precise interpretation of the second part that has led to the inconsistencies of interpretation between member states.
2. If medicinal claims are made based on its traditional use as defined in Directive 2004/24/EC on traditional herbal medicinal products, or the herb is considered medicinal by function the product may be categorized as a traditional herbal medicinal product, provided the time-related criteria are met (i.e. 30 years use).
3. If it is categorized as food or food ingredient. Article 2 of Regulation (EC) No. 178/2002 giving the definition of a food ingredient must be taken into consideration. For whole foods with benefits beyond basic nutrition (for example, whole grain oats for cholesterol lowering effect), the material must be well identified and characterized.
4. Novel Food Regulation (EC) No. 258/97 defines a novel food as foods or food ingredients, which have not been used to a significant degree for human consumption in the EU before 15 May 1997. (For example, Noni juice. Lycopene derived from *Blakeslea trispora*.) A comprehensive safety evaluation is required before approval for use in foods is given.

5. Directive 89/398/EEC defines foods for particular nutritional use (PARNUTS) as foods, "which, owing to their special composition or manufacturing process are clearly distinguishable from food stuffs for normal consumption, which are suitable for claimed nutritional purposes, and which are marketed in such way as to indicate such suitability". This category covers the dietetic foods. Examples are: infant formulae, baby foods for infants and young children, slimming foods, foods for special medical uses, sports foods, food for diabetics, etc.
6. Directive 89/107/EEC defines food additives as substances that are intentionally added to foods to perform certain technological functions such as to colour, or to preserve. Processing aids are not, as yet, regulated as food additives and flavourings are the subject of specific legislation.
7. Food supplements are defined in Article 2 of Directive 2002/46/EC, as "Food stuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drops dispensing bottles and other similar forms of liquids and powders designated to be taken in measures small unit quantities". Examples are Pycnogenol® (French maritime pine bark extract), green tea extract or grape seed extract.
8. There is a regulation in progress for frame work legislation on "Nutritional and Health Claims for Food" and this is likely to be adopted early in 2006. The proposal of European Commission (EU Commission, 2003a) was made on 16.07.2003.
9. A regulation on food fortification (EU Commission, 2003b) with the formal title of "The Addition of Vitamins, Minerals and Certain other Substances to Foods" is at present under consideration by the European Parliament and the Council and could be adopted early in 2006.

   Chapter 3 of this proposal contains a regulatory structure for the control of substances, including botanicals, in foods other than food supplements. It is intended that there will be an annex containing a list of prohibited ingredients, one with a list of ingredients subject to controls on levels or other requirements such as labelling and a third contentious list of 'substances under scrutiny'. This third list is intended to contain substances for which safety concerns have been raised and which are required to be evaluated for safety by the European Food Safety Authority. EU Commission's proposal was published on 17 January 2003.
10. Use as a cosmetic agent as per Directive 76/768/EEC would put the herbal product into cosmetic category, as defined in the legislation.

3.1. Regulatory status and positioning of botanicals

3.1.1. Food supplement directive

Article 2a of Directive 2002/46/EC defines as Food Supplement, as described earlier at point 7 in Section 3.

As stated at paragraph 6 of the Recitals, Directive 2002/46/EC at present only covers vitamins and minerals, however, in the next few years the scope will be extended to include other ingredients that are present in food supplements including amino acids, essential fatty acids, fibres and various plants and herbal extracts.

According to Article 4.8: "Not later than 12 July 2007, the commission shall submit to the European Parliament and the Council, a report on the advisability of establishing specific rules, including where appropriate positive lists, on category of nutrients or of substances with a nutritional or physiological effect other than those referred to in paragraph 1, accompanied by any proposal for amendments to this directive which the commission deems necessary".

Since at present there is no formal legislation at EU level to regulate botanicals as foods or food supplements, some member states such as Belgium, The Netherlands and France have introduced controls under their national legislation.

3.1.2. Traditional herbal medicinal products directive

Directive 2004/27/EC on "Traditional Herbal Medicinal Products", introduces a simplified registration procedure, based on "traditional use" ensuring quality and safety, without the need to prove efficacy of the product. Community lists are being prepared for traditional medicinal herbs.

A large number of botanical materials (e.g. whole, fragmented or cut plants, algae, fungi, lichens), and botanical preparations obtained from these materials by various processes (e.g. extraction, distillation, purification, concentration and fermentation) readily find there way onto the food supplement market. From legislation view points as discussed earlier, herbal food supplement category has to be separately identified by carefully interpreting the data on physiological versus pharmacological and health versus disease conditions on dose/concentration basis, taking into consideration

the Directive 2002/46/EC on Food Supplements and Directives 2004/27/EC and 2004/24/EC on medicinal products and traditional herbal medicinal products, respectively.

"*Legislation always runs behind reality*". The problem of borderline botanical-sourced products is still not resolved and will remain unresolved, unless there is clear distinction between products defined as herbal/traditional herbal medicinal products (according to Directive 2001/83/EC or 2004/27/EC) and food supplements (according to Directive 2002/46/EC). Dr. Konstantin Keller (Keller, 2003), European Medicine Evaluation Agency (EMEA), quoted:

- "The definition of herbal medicinal product: any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations", ingredients at *pharmacologically active level*.
- Traditional herbal products containing a dose of herbal substances or herbal preparations which is *below pharmacological level*, will accordingly fall under food legislation.

  This means that same botanical-sourced product may be regulated under three legislations (Directives 2004/27/EC, 2004/24/EC and 2002/46/EC). According to Dr. Keller, the *presented claim*(*s*) *and the intended use*(*s*) will be the first decision points.
- The posology/dosage and possible *pharmacological actions* should be considered on the basis of original or bibliographic data as a second decision point:
  - If the posology is *equal or above* the pharmacologically active dosage demonstrated by the studies or by bibliography related to medicinal use, the product is likely to be classified as *medicine*.
  - If the posology is *lower* or if such data do not exist, the product may be classified as a *food supplement*, if the conditions as set out by Directive 2002/46/EC (e.g. safety, listing) and other relevant legislation related to food (e.g. evidence for claims) are met.

When is an herbal (*peppermint*) *tea a medicine and when it is a food*?

In the area of herbal ingredients, it is important to look at the claim, presentation and consumer's expectations.

Thus, "peppermint tea with a claim as refreshing beverage would be a *food* and with a claim of prevention/treatment of stomach upset a *medicine*".

Likewise, Senna tea with a healthy supper-time tea to help digestion claim will be considered as *medicine*. Here the objective of the claim is a pharmacological action corresponds to the expectations of the consumer (*Proceedings of AESGP Members Meeting*, *Vienna*, *16–18 January 2003*) (Keller, 2003).

Directives 89/398/EEC on "Food for special purposes" and Regulation (EC) No. 258/97 on "Novel Foods" that provide additional channel for some botanicals and botanical preparations further poses problem while carefully categorizing the botanicals under proposed positive listing to be annexed to Food Supplement Directive 2002/46/EC thus provides very limited opportunity.

Listings of respective products to be annexed to respective directives are still not completed/available to allow borderline issues to be easily resolved.

3.2. Regulatory status of botanical nutraceuticals as food supplements in the EU

Even after the introduction of the Food Supplements Directive 2002/46/EC, there is still very little harmonisation across the EU, particularly with regard to substances which are neither vitamins nor minerals. Botanical-sourced supplement ingredients are the subject of diverse national legislation. For example:

- Belgium has introduced both positive (permitted) and negative (prohibited) lists for plants, their derivatives and fungae. This list was amended in early 2005 to introduce maximum levels of active constituents or marker substances for a number of herbs and their extracts.
- In Germany almost all botanicals sold in unit dose form (i.e. as supplements) are considered medicinal and require medicines authorisation.
- In the United Kingdom a concession to sell certain medicinal herbs without licensing (Section 12.2 of the UK Medicines Act 1968) was removed from the 1 May 2004. From October 2005 only those botanicals officially defined by the British authorities as not being medicinal by function will be permitted in supplements and foods. Other products will require either registration under the Traditional Herbal Medicinal Products Directive or full medicines authorisation.
- France has officially only 34 botanicals permitted for use in foods with a further list of over 100 which can be registered under a procedure similar to that required from 2005 for traditional herbal medicinal products.

- The Netherlands is now regarded as having the most liberal regulatory regime with the only controls currently being a relatively short negative list of dangerous herbs.
- Italy has a list of notified herbal food supplement products and another list of herbals prohibited to be incorporated in food supplements.

This disparity in approach results in products having to be assessed for legality in each country. For some herbs the national requirements are very different such as in the classification of *Ginkgo biloba* which can be sold as a food supplement in the United Kingdom and Netherlands, as a registered OTC medicine in Germany and France but only as a 'prescription only' medicine in Ireland.

3.3. Regulatory status of botanical-sourced nutraceuticals as food ingredients in the EU

When considering the use of botanical nutraceuticals in foods in the EU there are a number of issues in addition to those already discussed.

The two most important are the novel food status and whether the ingredient could be deemed to be 'medicinal by function'.

Although the Regulation on Novel Foods and Novel Ingredients came into force in early 1997 it was almost 7 years later that the European Commission introduced a change in the interpretation of the regulation. This change was ratified by the EU Standing Committee on the Food Chain and Animal Health in February 2005.

The result of this change is that the pre-1997 use in food supplements only does not confer exemption from the regulation for use in other food categories.

This means that if a nutraceutical can only be demonstrated to have been used in supplements in the EU before May 1997, any intention to use it in a drink, for example, would require a novel foods application and official approval. The application must include a comprehensive range of toxicity studies. If the ingredient was in use in supplements only before 1997 there is a high probability that extra data will be required to sustain an application for food use.

In addition to the novel food status of a nutraceutical ingredient intended for use in a food, it is important that the type of ingredient and levels of anticipated consumption do not classify it as being 'medicinal by function'. Such a classification would preclude its use in foods.

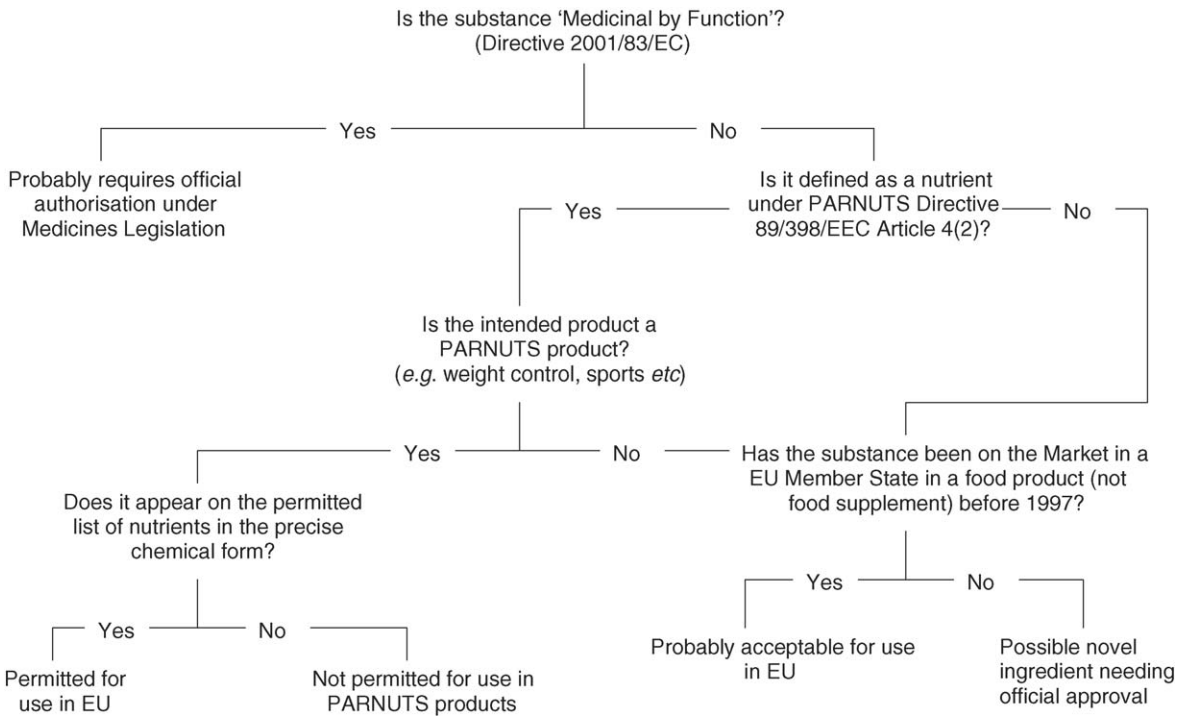

Fig. 2. Decision tree to determine the status of an ingredient.

If the product falls into the classification of a dietetic food (Directive 89/398/EEC) further controls may apply.

A decision tree is given in Fig. 2.

3.4. Regulatory status of botanical-sourced nutraceuticals as functional foods in the EU

The concept of foods for specified health use (FOSHU) was established (The FOSHU system, 1991) in Japan in 1991.

"Foods that are expected to have certain health benefits, and have been licensed to bear a label claiming that a person using them for a specified health use may expect to obtain the health use through the consumption thereof".

According to Japanese Ministry of Health and Welfare FOSHU are:

- foods that are expected to have a specific health effect due to relevant constituents, or foods from which allergens have been removed;
- foods where the effect of such addition or removal has been scientifically evaluated and permission is granted to make claims regarding their specific beneficial effects on health.

According to European consensus (Diplock et al., 1999) the unique features of functional foods are:

- conventional or everyday food;
- consumed as a part of the normal diet;
- composed of naturally occurring component, some time in unnatural proportions;
- having a positive effect on the "target function" beyond nutritive value (basic nutrition);
- may enhance well being and health and/or reduce the risk of disease or provide health benefits so as to improve the quality of life including physical, psychological and behavioural performances;
- having authorized and scientifically substantiated health claims.

It is in that general context that the European Commission's concerted action on Functional Food Science in Europe (FUFOSE), actively involving large number of the most prominent European experts in nutrition and related sciences were engaged by the International Life Science Institute (ILSI) in Europe (Diplock et al., 1999).

In this context, "target function" refers to genomic, biochemical, physiological, psychological or behavioural functions that are relevant to the maintenance of a state of well being and health or to the reduction of the risk of a disease. Modulation of these functions should be quantitatively/objectively evaluated by measuring the biochemical markers (e.g. metabolite, specific proteins, hormone, enzyme, etc.) or physiological parameters (e.g. blood pressure, heart rate, gastrointestinal transit time, etc.), changes in physical and intellectual performance using objective parameters (Diplock et al., 1999).

3.4.1. EU legislations and functional foods

Food law always lags behind innovation and developments, sometimes by more than a decade. This is particularly true in case of functional food, which is still in a state of taking its shape in the frame work of European legislation. Within Europe there has been increasing recognition of functional foods by national health authorities, particularly in the area of health claims (discussed later in a different section).

The term 'Functional Food' embraces a wide range of products from bio-active dairy products to drinks containing antioxidants.

A food can be regarded as 'functional' if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond normal and adequate nutrition, in a way that improves health and well being or reduces the risk of disease.

Current EU legislation does not recognise functional foods as a distinct category of foods, as for example in Japan. This means that functional products must comply with all relevant food legislation with respect to composition, labelling, claims, etc. A legal definition for functional foods is not in place in Europe, nor is there any specific regulatory control on health claims (Richardson, 1996). The UK Ministry of Agriculture, Fisheries and Food (MAFF) developed a working definition, which is "a food that has had a component incorporated into it to give a specific medical or physiological benefit, other than a purely nutritional effect". This definition distinguishes functional foods from those that are fortified with vitamins and minerals and from food supplements (MAFF, 1995).

3.4.2. EU legislations and foods for particular nutritional uses (PARNUTS)

The EU PARNUTS Directive 89/398/EEC was designed to meet the particular nutritional requirements of certain categories of populations. The definition of PARNUTS Foods has been stated earlier.

There are six categories of PARNUTS Foods:

1. *Infant formulae and follow-on formulae* are governed by Directive 91/321/EEC.
2. *Processed cereal-based foods and baby foods for infants and young children*. This category of PARNUTS Foods is governed by Directive 96/5/EC.
3. Foods for energy-restricted diet (*sliming foods*) are governed by Directive 96/8/EC.
4. *Dietary foods for special medical uses* (*medical foods*) are governed by Directive 1999/21/EC.
5. *Sports foods*: Directive is in development phase.
6. *Diabetic foods*: Directive is in development phase.

The list of permitted PARNUTS ingredients is attached as Annex 2 of Directive 2001/15/EC. Rules relating to their specific compositional details and labelling requirements are however still subject to the National Regulation in different EU countries. There are six categories of listed substances:

1. vitamins
2. minerals
3. amino acids
4. carnitine and taurine
5. nucleotides
6. choline and insitol

Applications can be made for additions to the list but have to be supported by a comprehensive safety dossier which is assessed by the European Food Safety Authority (EFSA).

Finally there are non-listed substances belonging to non-existent ingredient categories (fatty acids and botanical) products. There are no harmonized EU rules for these substances. The permitted use as a PARNUTS Food containing other ingredients is decided at national level.

PARNUTS Foods have well-defined general labelling provisions and in addition those specified in directives relating to different categories of PARNUTS Foods.

There are well-defined PARNUTS authorization procedures.

3.4.3. EU legislation and novel foods

The European Commission introduced in 1997 Regulation (EC) No. 258/97 concerning novel foods and novel food ingredient. For definition see point 4 of the regulatory frame work in Section 3 of this article.

There are six categories of foods or food ingredients:

1. containing or consisting of GMOs;
2. produced from (but not containing) GMOs;
3. consisting of or isolated from micro-organisms, fungi or algae;
4. consisting of or isolated from plants, and ingredients isolated from animals (except those obtained by traditional propagating or breeding practices and having history of safe food use);
5. have a new or intentionally modified primary molecular structure;
6. have been subject to a new production process resulting in significant changes in the composition or structure of foods/food ingredient, which affects the nutritional value, metabolism or level of undesirable substances.

From 1 May 2004 the first two categories were transferred to Regulation (EC) No. 1829/2003 on genetically modified foods.

The Novel Food Regulations have well-defined authorization procedures leading to marketing authorization on a Pan-European basis.

4. Quality aspects

The botanical product should be well identified and characterized. Identification, standardisation and specification are of paramount importance in considering the safety of botanicals (Schilter et al., 2003). Here are few points to consider for reference: the botanical source, growth conditions, raw material, manufacturing process, botanical preparation and end product. The variability of the plant material is due to different growth, harvesting, drying and storage conditions (Bauer, 1998). Standardised conditions of cultivation in the form of good agriculture practice (GAP), is essential. With reference to extracts the polarity of solvents, the mode of extraction, and instability of constituents may also influence the composition and quality of the extracts (Bauer, 1998).

Points to consider:

1. *Botanical source*:
   - identity, scientific name, common name;
   - part of the plant used;
   - geographical origin;
   - contamination with other plant species: species identification is a critical factor, where related or toxic species/genera are known;
   - chemical and microbial contamination and foreign matter, such as heavy metals, pesticide residues, aflatoxins and radioactivity;
   - part of the plant as a source of the material: if toxic constituents are present in higher concentration in

a part of the plant that is not normally consumed (e.g. Comfrey roots contains higher concentration of pyrrolizidine alkaloids than leaves).

2. *Growth conditions*:
   - good agriculture practice;
   - wild or cultivated;
   - site of collection;
   - time of harvest;
   - stage of growth;
   - storage conditions post-harvest;
   - pre- and post-harvest treatments (use of pesticides, etc).
3. *Raw material*:
   - specifications according to standard method (Pharmacopoeia) or validated standard method;
   - quantitative test to determine constituents relevant to their biological significance;
   - stability data.
4. *Raw process applied to starting material*:
   - extraction process;
   - solvents;
   - methods used;
   - specific precautions (light temperature sensitivity).
5. *Botanical preparation*:
   - standardization criteria (markers, other relative constituents, plant extract ratio);
   - specifications (level/range of markers);
   - physiochemical properties (stability data);
   - purity criteria;
   - biologically active principles (in flavouring legislation) limits to be respected as per regulations;
   - level and nature of excipients;
   - formulation methodology;
   - storage conditions.
6. *End product* (*food supplement containing botanical preparation*):
   - fate in the formulated product;
   - preparation for consumption;
   - stability data.
7. *Specifications*:
   - Scientific quality of the data: The analysis of findings on which the judgment is made, experimental design statistics used and rational for conclusions.
   - Quality control/assurance (methods of production, specifications) should guarantee for its appropriate intended use. Batch to batch analysis data.
   - Standardization to comply with existing standards based on phytochemical markers or fixed plant/extract ratio (PER). Constituents known to be responsible for adverse effects should be included in criteria of standardization. If appropriate markers are not known, chemical finger prints are useful such as HPLC, HPLC-MS and HPLC-UV.
   - Human safety data takes priority over non-clinical safety data.
   - Non-clinical testing should focus on toxicology studies that are difficult to detect clinically.
   - Products with well-established use have an established efficacy and an acceptable level of safety substantiated by available scientific data.
   - Post-marketing surveys (quality and technical aspects) should be considered routine for botanical products.
   - Adverse events reporting.
   - If authorities or manufacturer as a result of new information gets convinced that a botanical product endangers human health, this should be brought to public domain and use of such products should be suspended or restricted.
   - Health authorities and manufacturer of product should share the responsibility to take appropriate and objective measure to give update information to the consumers.
8. *Other technical criteria*:
   - Impact of production process:
     a. use of solvents;
     b. ratio of solvents.
   - Compositional variability: The problem of compositional variability has been highlighted in the case of ginseng dietary supplements.
   - Consistency of batch to batch analysis data: is essential for product standardization. Standardisation may be based on level of one or several active constituents. Active chemical fingerprints would be required with limits on the range of variations.
   - Fixed plant/extract ratio (PER).
   - Solvent residues.
   - Pesticide residues.
   - Stability data.
   - Purity criteria.
   - Storage conditions.
   - Fate in the formulated product, etc.

5. Safety studies

5.1. In vitro safety data

These include isolated cells, microorganisms, subcellular components (enzymes, receptors and DNA). These models are rapid, less expensive and reveal mechanisms of actions.

Guiding Principle for the in vitro study data can: serve as signals of potential harmful effects in human, but not

as independent indicators of risk unless an ingredient causes an effect that has been associated with harmful effect in animals or human and there is evidence that the ingredient or its metabolites are present in physiological sites where they could cause harms. Alone, in vitro study should serve only as hypothesis generators and indicators of possible mechanisms of harm when the totality of the data from different key factors is considered.

5.2. *In vivo animal safety data*

Animal studies serve as important signal generators and in some cases, may stand alone as indicators of unreasonable risks. These include acute, sub-chronic, chronic toxicity, reproduction toxicity, in vivo genotoxicity and safety pharmacology studies. Knowledge of an ingredient's pharmacokinetics and in vivo metabolism will allow most appropriate interpretation of relevancy of the dose used in the in vitro tests. All cells react differently to its unique biochemical pathways.

Guiding Principle of animal data is: even the absence of human adverse events, evidence of abnormalities from laboratory animal studies can be indicative of potential harm to humans. This indication may assume greater importance if the route of exposure/administration is similar (e.g. oral), the formulation is similar, and more than one species show the same toxicity.

Biologically activity of structurally related or taxonomically related substances: if the biological activity of related substances suggests concern that the food supplement ingredient may be harmful, these concerns should be considered.

- Structurally related substances.
- Computer programmed designing predicting biological activities of pure compounds.
- Chemical composition of botanical ingredients. For example, presence of:
  1. alkaloids;
  2. cardenoloids;
  3. colchicines-like compounds;
  4. cyanide containing compounds;
  5. nitrophenenthress;
  6. nitromines;
  7. phorbol esters;
  8. pyrrolizidines;
  9. urushiol-related compounds.

5.3. *Clinical safety data*

Vulnerable sub-groups: vulnerable subpopulations can be defined as groups of individuals who are more likely to experience an adverse event related to the use of a food supplement or ingredient or an individual in whom such events are more likely to be serious in comparison with the general population.

Characteristics of such vulnerability may be:

- Physiological (capacity of digestion, metabolism and excretion). Elderly population, children, age related changes, pregnancy.
- Disease related (hepatitis, renal disease may alter xenophobic clearance, hypertension, diabetes).
- Therapeutic intervention (AIDS patients on drug combinations that may alter cytochrome P450 activity).
- Drug, food supplements interactions (Vitamin E with Statin drugs).

Guiding Principle of clinical data is: as a Guiding Principle, when data indicate that an identifiable subpopulation may be especially sensitive to adverse effects from certain supplement ingredients, then this higher level of concern should be taken into account when screening the food supplement/ingredient.

6. Efficacy studies

6.1. *Health claims and their substantiation*

The important objective for the development of European legislation on health claims is to ensure that claims for food components and nutraceuticals are properly justified and they are scientifically substantiated (Byrne, 2003). A final proposal for a regulation of the European Parliament and the European Council on nutrition and health claims made for foods is expected to permit the use of "health claims" and "reduction of disease risk claims" for foods outside the scope of medicinal law, and Article 6 sets out the general principles for substantiation. Health claims will therefore only be approved for use on labelling, presentation and advertising of foods in the EU market after a scientific evaluation of the highest possible standard. Currently, the proposed legislation states that in order to ensure harmonized scientific assessment of a health claim, the European Food Safety Authority should carry out the assessments.

It is anticipated that for long-established and non-controversial science, e.g. health claims that describe the role of a nutrient or another substance in growth, development and normal physiological functions of the body, the assessment and approval prior to their use, will result in the compilation of an approved list within a 3-year period of the entry into force of the regulation (and

that the EU will develop a register of such health claims (generic health claims)).

For all other "product-specific health claims", an authorization procedure will be developed based on substantiation by generally accepted scientific data.

Whatever regulatory frame work on this aspect may develop, it will need to protect consumers from false and misleading claims and to satisfy the need of industry for innovation in the production, development, marketing and promotion of foods. Consumers must develop strong confidence in the scientific regulatory process used to support the approved health claims.

6.2. PASSCLAIM initiative

The International Life Science Institute (ILSI Europe) initiated the concerted action supported by the European Commission on "Process for the Assessment of Scientific Support for Claims" (PASSCLAIM). PASSCLAIM is built on concerted action by Functional Food Science in Europe (FUFOSE), which suggested claims for "enhanced function" and "reduced risk of disease", should be based on sound scientific evidence, using appropriate validated biomarkers (Bellisle et al., 1998). The FUFOSE consensus document was published in the *British Journal of Nutrition* (Diplock et al., 1999).

6.3. Process for scientific validation and substantiation of health claims

The objectives are to identify common new ideas, definitions, best practice and methodology to underpin current and future regulatory developments (Richardson et al., 2003). The PASSCLAIM initiative and proposed draft regulations have defined two broad categories of claim:

- "*Nutrient content claims*" based on what the product contains (e.g. good source of fibre, which will be restricted to foods containing 6 g of fibre per 100 g).
- "*Health claims*" relating to health, well being and/or performance, including well established:
  - *Nutrient function claims* describe the role of a nutrient in normal human physiology that is based on long-established, non-controversial science (e.g. "calcium helps build strong bones", "antioxidants protects against oxidative stress"). This category of health claims would be established within 2 years after the regulation is enacted by compiling the list of these claims from member states, which would be reviewed and approved by the European Food Safety Authority.
  - *Disease risk reduction claims* that a substance may reduce the factors known to be implicated in the risk of disease development (e.g. "calcium may reduce the risk of osteoporosis"). This category of claims would be based on the review and approval of a scientific dossier in support of the relationship between the product and the disease risk reduction claim by EFSA.

On qualification terms these are:

Generic claims mean any claim that relates to diets, broad food categories, foods, herbal products and food components. The claim is based on knowledge from evidence generally available in scientific literature and/or recommendations from national or international public health bodies. A "complying" botanical preparation should contain the components in sufficient quantity to produce the effect claimed, or falls with in category of botanical component to which the generic claim applies.

Product-specific claims mean having a specific relation with a particular botanical product. The product has been designed and formulated to provide a specific well-documented effect. For all "product-specific health claims", an authorization procedure will be developed based on substantiation by generally accepted scientific data. Each product has to be evaluated case by case.

Medicinal claims mean that a nutraceutical (food or food component) has the property of treating, preventing or curing human disease or making any reference to such property. These claims are prohibited absolutely in the labelling or advertising of foods in current EU legislation (Directive 2000/13/EC).

6.3.1. Criteria for scientific substantiation

- The food or food component, including botanical product/ingredient to which the claim is attributed should be well characterised.
- Substantiation of a claim should be based on human data, primarily from well-designed intervention studies considering target population, appropriate controls, adequate duration of exposure and follow-up to demonstrate the intended effect.
- Generally accepted scientific data must be systematic and objective, balanced and unbiased, strong, consistent and reproducible, with appropriate statistical analysis.
- The data should be based on validated and predicted biomarkers for:
  - enhanced function;
  - disease risk reduction.

- The overall assessment should be based on the application of scientific judgment and critical interpretation of the data as a whole.

The claims on the positive list (generic claims) must be based on and substantiated by "generally accepted scientific data" and the person or company placing the product on the market may be required to produce all relevant elements and data establishing compliance with the regulation.

6.3.2. Authorizing bodies and grading of qualifications of health claims

The preamble of the proposed EU legislation states that health claims should only be authorized by EFSA after scientific assessment of the highest possible standard. There is no dispute about this, but the major concern is how to accommodate the emerging science in an appropriate grading system. WHO and WCRF have established four grades of evidence: "convincing", "probable", "possible" and "insufficient". These correspond to the four levels of qualified health claims proposed in the USA. The first level "convincing" means convincing scientific evidence. The second level "probable" means that although there is scientific evidence supporting the claim, the evidence is not conclusive. The third level "possible" means "some scientific evidence suggests that however, the evidence is limited and not conclusive". The fourth level "insufficient" means "very limited and preliminary scientific research suggests, there is little scientific evidence to support the claim".

The EU has not yet considered the concept of grades of evidence, but it is crucial to support scientific initiatives to find an approach where the term "generally accepted scientific data" include not only generic or well-established linkage between food and food components and health benefits, and to establish standards which should not be revoked or reversed by emerging science at a later stage.

Efforts are in progress to explore and develop different wordings on the level of certainty of the scientific evidence, which is of paramount importance.

7. Conclusions

The addition of botanical-sourced nutraceuticals to food supplements and functional foods encompass a number of issues.

The predominant one is the status of the food or ingredient in relation to EU legislation covering both medicines and foods, as many of the ingredients are very close to the borderline between the two classifications.

Although new legislation covering traditional herbal medicines is now in force, the work on the control of botanically derived substances and particularly herbs, in food supplements and other foods has barely started and controls of these ingredients in food supplements are now unlikely to be in place before 2012. In the meantime companies wishing to market products in the EU will have to continue to assess their regulatory status in each member state.

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