EFFICACY AND SAFETY REGULATIONS AND SCIENTIFIC CRITERIA APPLICABLE TO TRADITIONAL BOTANICAL FOOD SUPPLEMENTS AND HERBAL MEDICINAL PRODUCTS MARKETED IN THE EUROPEAN UNION

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Muenster, 1° September 2013

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- This presentation does not reflects the viewpoints of EFSA, but only those of the Author.

Botanicals and botanical preparations contain many different biologically-active substances

- Many substances with largely different therapeutic activities (e.g. amino acids, alkaloids, cardiac glycosides, mono-, di-, tri- and sesquiterpens, phenolic compounds,coumarins and enzymes) have been identified in a variety of common botanical species. About 40% of current mono-molecular medicines derive directly or indirectly from botanicals species.
- Many nutrient substances are also known to be present in botanicals species (e.g. vitamins , minerals, and many substances with physiological effects), helping the human body in maintaining its homeostasis. Moreover, some recognized therapeutic substances may, at low concentrations, exert a homeostatic effect rather than a therapeutic effect.

Botanicals and botanical preparations contain many different biologically-active substances

- Highly heterogeneous preparations obtained from many different botanical species and parts have been used for long time and currently continue to be used with the objective of:
  - correcting altered physiological processes in case of diseases or preventing their oc-curence (traditional herbal medicinal pro-ducts- THMP);
  - helping the human body in maintaining its homeostasis, i.e.normal functioning of phy-siological processes (traditional plant food supplements- TPFs);

often without the identification of the nature of the components relieving/preventing disease symptoms or exerting homeostatic effects

Traditions of use of botanical products are very different in different countries

- Herbal products have become traditional in the European Member States (MSs) often under no *ad hoc* regulation, depending on the country's availability of botanicals, on prevalent medical and nutritional practices, as well as on cultural, technological and social factors.
- Therefore, the development of national practices/regulations on these botanical products in the 20th century was in all MSs mainly based on the long term tradition of use and it resulted quite different in different countries for the above-mentioned reasons.
- The European Institutions have started their action for harmonizing applicable regulations and scientific criteria to botanical products only recently and with a limited success so far.

Initiatives of the EU institutions to harmonize regulations on botanicals

- The framework legislation (Directive 2002/46/ EC) on food supplements, including the botanical ones, was adopted in 2002, whereas the nutrition and health claims were only regulated in 2006 (Reg. (CE) 1924).

- The *ad hoc D*irective for traditional herbal medicinal products (THMP) (Directive 2004/24/EC) was formally adopted only in 2004 .

Traditional botanical products intended to modify, to correct or to restore organic human functions should fall under the regulation on medicinal products (THMP).

- **Under Directive EC/24/2004, to register a THMP, it has only to be demonstrated that the product is "non toxic under the specific conditions of use and the pharmacological effects and efficacy are plausible on the basis of long term use and of available esperience".**

- **A *"facilitated registration"* for oral, external or inhalation administration can be released at MS level for products already present on the market for 30 years, of which 15 in an EU MS, even if the product has been marketed without a specific authorization.**

Registration of traditional herbal medicinal products

- The registration as THMP is considerably simplified if the product is included in the Community List of substances, preparations and their combinations for the use in THMP,sistematically updated by the competent EMA Committee , or an *ad hoc* monograph has been produced by this Committee.
- By 31 December 2011, 751 registrations were granted in the EU MSs. The countries with most registrations were: Poland (164), UK (150), Germany (107) and Austria (92). The top therapeutical areas were:cough and cold; gastro-intestinal disorders and mental stress and mood disorders.

Safety and effficacy of TPFS

- **Traditional botanical food supplements are concentrated sources of nutrients or of other substances with a nutritional or physiological effect, regulated by the Directive 2002/46/ CE that harmonizes, at an European level, general definitions, labelling, publicity and vitamins and minerals used, but not the marketing procedures;**
- **Decisions on safety and efficacy of food supplements, including the botanical ones, have depended for long time mainly on manufacturers, whereas EU Member States competent Authorities have supervised the market according to their own criteria which are not harmonised at the EU level.**

The current Regulation on marketing of Food Supplements in Member States

- **In some (but not all) EU Member States, food supplements must be notified before marketing and only botanical substances and preparation listed in an *ad hoc* Annex can be used in food supplements;**
- **The principle of mutual recognition is applied to food supplements in compliance with regulations in EU Member States ;**
- **Many claims have been used so far on these products, but now they will have to be approved, according to Reg. EC 1924/2006, at an European level (Art. 13(1)Procedure of Reg.EC 1924/2006) or dismissed.**

Table 1. Examples of different national approaches for the marketing of selected botanicals in MSs of the EU

- 1.*Alium sativum* (AU, BE and It-Permitted as food supplement ; BL and CY-an authorization is needed for each product; Czech Rep., DE and IR-Permitted with specific prescriptions ; FR-Not permitted, but it could authorized ; SP e SW- It is considered a medicinal product).
- 2. *Ginkgo biloba (*IT,NL and PL- Permitted as food supplement; DE,GR,IR, SL, SP and SW- Not permitted as it is considered a medicinal product; BE, Czech Rep. and HON- Permitted, but only within maximum levels.

Conclusions on safety of botanical food supplements at national level in the EU are contradictory and conflicting

According to documents officially published , out of about 1900 herbal species (AESGP, 2007),several hundreds botanical species are:

- prohibited from use in some M.S. and not regulated in other;
- allowed for use in some M.S., prohibited in other M.S. and not regulated in other M.S.; or
- allowed for use in some M.S. and not regulated in other M.S.

A harmonized procedure for safety assessment has been produced by EFSA

- A guidance document to assess safety of botanical food supplements, based on traditional use, has been produced by EFSA, together with a Compendium to identify botanical species and varieties containing substances of concern which deserve a different approach, has been adopted in 2008 and tested in 2009.
- The Compendium(version II adopted in 2012) lists a very large number of botanical genus, species and varieties reported to naturally contain toxic, addictive, psychotropic, or other substances of possible concern and identify them and the plant parts where they occur.

More EFSA on going work on TPFS safety

- EFSA has requested the Scientific Committee to update the Compendium of botanicals reported to contain inherent substances of possible concern for human health that is available on the EFSA website. The resulting version N°3 of the Compendium, currently in preparation, will:
- (i) Be expanded with botanicals used in the non-European countries or marketed in the European Union which have not been considered in the previous versions of the Compendium;
- (ii)Provide information on target organs, mode of action and toxic/adverse effects in a systematic manner;
- (iii) Be built in a database format, searchable on the EFSA website and compatible with the EFSA chemical hazard database.

More EFSA on going work on TPFS safety

- Another SC working group has been established to develop the guidance on a safety assessment procedure for botanicals and botanical preparations intended for use as ingredients in food supplements, which foresees that botanicals or botanical preparations for which an adequate body of knowledge exists could benefit from a "presumption of safety" without any need for further testing.
- Some outsourcing is also taking place to support the on going heavy work of EFSA on botanicals.

Regulation EC 1924/2006 on nutrition and health claims

- Another critical issue for botanical food supplements is related to voluntary nutritional and health claims that have to comply with Regulation 1924/2006, i.e. they have to be authorized case by case, based on EFSA's evaluation of " generally accepted scientific data» .
- Moreover, according to such a Regulation, generic claims, which are quite important to inform consumers on the benefit of food supplements have to be well understood by the average consumer.
- However, most of the claims on botanical food supplements proposed so far have not been considered by EFSA as being scientifically substantiated.

BOTANICAL CLAIMS EVALUATED BY EFSA IN THE FIRST BATCH

- *Cyamopsis tetragonoloba* (glycemia) ……NSC;ND
- *Equisetum* (skin, hairs and bones)…….. NS*C;*ND
- Eq*uisetum arvense* (body weight)…… NSC;ND
- *Daucus carota (*vision*)…….* NSC;ND
- *Viola tricolor* (irritation) ……. NSC;ND
- *Undaria pinnatifida* (body weight)…… SC;*ND*
- *Theobroma cacao* (body weight)…… SC;ND
- *Fagopyrum esculentum* (TRS)……NSC;*ND*
- *Tussilago farfara* (TRS and immune-system) ……..NSC;ND
- *Aegopodium podagraria* (normal body weight)……NSC;ND
- *Lathyrus pratensis* (TRS)…….. NSC;ND
- _____
- NSC= Not adequately characterized
- ND= Not demonstrated

BOTANICAL CLAIMS EVALUATED BY EFSA IN THE FIRST BATCH

- *Levisticum officinale* (diuresis)… ……SC;ND
- *Armoracia rusticana* (diuresis)…….. SC;ND
- *Justicia adhatoda* (oxidative damage) …….. .NSC;ND
- *Calluna vulgaris* (umore e sonno)…… …. SC;ND
- *Carthamus tinctorius* (skin and hairs)……SC;ND
- *Ocimum basilicum* (diuresis)……SC;ND
- *Chenopodiyum quinoa* (hairs)…… …… NSC;ND
- *Aiuga reptans* (sebum production)…… .. NSC;ND
- *Perna canaliculus* (joints,bones and muscles)……. NSC;ND
- *Hibiscus sabdariffa* (diuresis and intestinal func.) …. SC;ND
- *Angelica sinensis* (joints and oxigen transport)… .NSC;ND

NSC= Not adequately characterized

ND= Not demonstrated

BOTANICAL CLAIMS EVALUATED By EFSA IN THE FIRST BATCH

- *Justicia gendarussa* (diuresis and urinary infections).- NSC;ND
- *Helianthus tuberosus* (body weigh, lactose degradation, patogenic microrganisms)…… SC;ND
- *Picea albies* (irritation TRS)…… ……..……..SC;ND
- *Corylus avellana* (skin)……..……NSC;ND
- *Amni visnaga* (irritation TRS)…… ……..SC;ND
- *Fraxinus excelsior* (joints and body weight)… ……SC;ND

NSC= Not adequately characterized

ND= Not demonstrated

Regulation EC 1924/2006 on nutrition and health claims

- As a consequence, the European Commission has requested EFSA to suspend the evaluation of botanical claims. For the time being the botanical claims are still in use, but a (negative) decision is pending and may arrive at any time.
- Although the lack of claims does not prevent botanical food supplements from being marketed, it remains a major problem for the consumer to under-stand, in the absence of claims, the benefits, if any, associated with the consumption of the product.
- The pending question here is why the more tolerant regulatory approach adopted by Directive 2004/24/EC for THMPs to take into account specificities of botanical products has not been followed also for THFSs ?

Overlaps of THMPs and TPFSs

- The distinction and separation of the botanical species used as traditional food supplements and medicinal products in EU Member States is highly problematic. In fact, a number of botanical species used under a specific regulatory domain(e.g. food supplements) are also used in the other domain (e.g. traditional medicinal products) with a very broad overlap.
- A study on 171 botanical species carried out in 2010.

Double traditional uses of individual botanical species as food medicinal products and food supplements

Botanical species	*Community List of traditional medicinal products*	*AESGP Food Supp. use catalogue (No. of countries)*
Calendula officinalis	*Yes*	*8*
Echinacea purpurea	*Yes*	*7*
Eleutherococcus senticosus	*Yes*	*5*
Foeniculum vulgare var. dulce	*Yes*	*7*
Foeniculum vulgare var. bitter	*Yes*	*7*
Linum usitatissimum	*Yes*	*6*
Pimpinella anisum L.	Yes	8
Mentha piperita	Yes	7
Valeriana officinalis	*Yes*	*2*

Double traditional uses of individual botanical species as food medicinal products and food supplements

Plant(s) –mono	No of products registered	Known food supplement use (AEGSP inventory)
Pelargonium sidoides	21	in 5 countries
Echinacea purpurea	17	in 7 " limit.
Harpagophytum procubens	12	in 7 " limit.
Valeriana officinalis	11	in 8 " limit
Hypericum perforatum	9	in 7 " limit.
Passiflora incarnata	7	in 11 " limit.
Arnica montana	5	in 3 " limit.
Rhodiolae roseae	4	in 6 " limit.
Salvia officinalis	3	in 8 " limit.
Tanacetum parthenium	3	in 5 " limit.
Aesculus hippocastanum	2	in 4 " limit

Food supplement use in different countries of traditional botanical species with an EMEA Monograph concerning medicinal use

- *Echinacea pallida (4);* - *Sambucus nigra (9);*
- *Equisetum arvense (7);* - *Solidago spp (3);*
- *Melilotus officinalis (4);* - *Betula spp (6)*
- *Plantago ovata (7);* - *Centaure cyanus (7)*
- *Primula spp (5);* - *Harpagophitum procumbens (2);*
- *Frangula purshiana (2);* - *Polypodium vulgare (3)*
- *Salix alba (4);* - *Ruscus aculeatus (4);*
- *Urtica spp (4);* - *Thymus spp (3);*
- *Aloe vera (7);* - *Verbascum spp. (6)*
- *Althea officinalis (6);* - *Melissa offcinalis (8)*
- *Avena sativa (8);* - *Passiflora spp (3)*

In parenthesis the number of countries in which the botanical species is used as food supplements

Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications) that are also as food supplements in other European countries

- AU: *Passiflora incarnata-uneasiness, stress, sleeping disorders and agitation (4); Pelargomium sidoides- cold (5); Arnica – muscles and joints ; Capsicum- muscles and joints (3); Rhodiolae rosa-stress (4); Harpagophytum procumbens- rheumatic pain (7).*
- FI: *Gingo biloba- cold hands and feet due to mild bloodflow disruption in periferal vessels (2).*
- DE: *Melissa officinalis- nervousness, tension, anxiety and headaches (8); Crataegus spp-circulatory functions; Levisticum officinale (8) plus Centaurium erythraea (8) and Rosmarinus officinalis (8)- inflammatory diseases of the lower urinary tract and decrease of kidney stones(8); Graminis- ; Valeriana -stress and sleep(2).*
- *GR: Harpagophytum procumbens-minor articular pain(7); Eleutherococcus senticosus – asthenia due to fatigue and weakness (5).*

- In parenthesis the number of countries in which the botanical species is used as food supplements

Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications) that are also as food supplements in other European countries

- NL: *Pelargonium sidoides- cold (5)* ;
- SR: *Crataegus spp. (8) plus Melissa officinalis (8) and Valeriana(2) - support of cardiovascular system under stress and convalescence;*
- *SL: Crataegus spp. (8)-support of cardiac and circulatory functions; Crataegus spp. (8) plus Passiflora spp.(4)- support of cardiac and circulatory functions and mild nervous heart complaints; Primula spp (5) plus Thymus (3)-cold; Plantago spp (6) plus Malva sylvestris (6)- cold; Valeriana (2) plus Melissa spp (8), Mentha piperita (7) and Lupulus- mental stress and aid sleep;*

- In parenthesis the number of countries in which the botanical species is used as food supplemennts

Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications that are also as food supplements in other EU countries

- SP: *Arnica montana-muscular aches, pains and stiffnes, sprains, bruises and swelling after contusions;*
- *SW: Rhodiola rosea (3)- fatigue and sensation of weakness; Pinus mugo(4) plus Citrus limon (5), Illicium verum (6),Foeniculum vulgare (7); Eucalyptus globulus (6), Mentha piperita (6), Thymus vulgaris (5), Tilia cordata (5), Pimpinella anisum (8), Carum carvi (8), Polygonum aviculare (4) – cold symtoms and occasional cough.*

- In parenthesis the number of countries in which the botanical species is used as food supplements

Botanical species registered in selected countries under Directive 2004/24/EC (and relative indications) that are also as food supplements in other European countries

- UK: ***Arnica montana – see SP*; *Harpagophytum procumbens-minor articular pain(7); Tanacetum parthenium (5)- migraine headaches;Cimicifuga racemosa (2)-symptoms of the menopause; Serenoa repens (6)- benign prostatic hypertrophy;Vitex agnus castus-sleep disturbances; Valeriana officinalis (2)-sleep disturbances; Aesculus hippocastanum-low mood and mild anxiety; Pelargonium sidoides (5)-cold; Echinacea purpurea (7)-common cold and influenza type infections; Rhodiolae rosa-stress (4); Hypericum perforatum (2)-low mood and slight anxiety.**

- In parenthesis the number of countries in which the botanical species is used as food supplements

Uptake of the traditional use registration scheme and implementation of the provisions of Directive 2004/24/EC in EU member States- Status 31 December 2011

- **The 10 most registered plants (used in mono-component products -246 over 375 registrations in 2011) are: *Hyperici herba;Pelargonii radix; Harpagophyti radix; Valeriana radix; Crataegi flium cum flore; Echinaceae purpureae radix; Hippocas-tanum semen; Passiflorae herba, Salvia officinalis folium and Melissae folium.***
- ***Clearly these botanical species find very large use also as food supplements.***

Annual sales (+)of traditional botanical products being marketed in selected countries as food supplements and medicinal products

Country	Botanical Food Supplements	Total (i.e. Botanical Food Supplements plus Botanical Medicinal Products)
▪ Italy	1454	1500
▪ Germany	841	2400
▪ France	532	1500

(+)Millions of euros

The EUROPEAN COMMISSION's REFLECTION PAPER

Just before the last summer break (in July 2012), the European Commission distributed among all Member States a reflection paper summarizing her perception of the current situation and asked for an opinion on what do next, offering the two following options :

- **Ask EFSA to resume its assessment of health claims on botanicals with no changes to the approach; or**
- **Recognise the peculiarity of the botanical case and address it through a review of legislation on botanicals.**

CONCLUSION 1

- **The nature of the commercial botanical products made available to consumers as traditional medicinal products or food supplements, currently depends, more than on the intrinsic properties of the botanical products and their constituent, mainly on the country under consideration as a consequence of how competent National Authorities and manufacturing companies interpret and apply current regulations rather than on objective criteria.**

Conclusion N.2

	Traditional Botanical Food Supplement	Traditional Botanical Medicinal Product
Safety	Uncertainty on how it is assessed. Comparability in different countries unknown.	Supported by EMEA Monographs or by *ad hoc assessment* case by case.
Efficacy with Claims	Generally accepted scientific data (generally unavailable)	Plausibility based on traditional use data
Efficacy without Claims/Indic.	Unclear	Impossible

- A number of traditional botanical products used indifferently as food supplements and traditional medicinal products.

Conclusion n.3

- It woud be advisable, in my opinion, that the European Commission and Member States, with the collaboration of EFSA and EMEA, undertake a new *ad hoc* collaborative effort to improve and further harmonize the current regulatory framework by developing:

  - a practical approach to better identify/characterize botanical species and preparations more suited for use as food supplements or medicinal products;

  - a balanced approach to safety and efficacy assessment of both typologies of products , preferably based on traditional use, to be used throughout the EU in a substantially coherent manner.

FINAL CONCLUSIONS

- 1. Botanical food supplements are intended to complement the normal diet, whereas medicinal products should be mainly intended for treating or preventing specific symptoms of disease;
- 2. Botanical food supplements could be for lifetime exposure, whereas this is not generally the case for medicinal products;
- 3. Even for products based on the same botanical species and parts of the plant, dietetic long-term use levels should likely to be lower that those applicable to medicinal products;
- 4. Indications of use for food supplements and medicinal products should be clearly different; EFSA and EMA should collaborate to help the European Commission to clearly establish such differences.

- **Part of this presentation has been published in an article entitled «Regulations applicable to plant food supplements and related products in the European Union» by V.Silano, P. Coppens, A. Larranaga-Guetaria, Paola Minghetti and R. Roth-Ehrang, appeared in Food Funct. 2011, 2, 710-718.**

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