NFI

CENTRO STUDI DELL'ALIMENTAZIONE
NUTRITION FOUNDATION OF ITALY

ASSOERBE SIAR SOCIETÀ ITALIANA ATTIVITÀ REGOLATORIE S.I.S.T.E.

Convegno

Prodotti di Origine Vegetale in Alimentazione, Erboristeria e Medicina: Aspetti di Sicurezza

Conference

Botanical Products as Food, Herbal Remedies and Drugs: Safety Aspects

Giovedì, 20 Novembre 2008

Centro Congressi Cariplo
Via Romagnosi, 6
Milano

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Botanical products are used as food, drugs and herbal remedies; these products fall, therefore, under different legal classifications and regulations.
This conference, promoted by NFI- Nutrition Foundation of Italy, together with ASSOERBE, Italian Association for Regulatory Activities – SIAR and Società Italiana delle Scienze e delle Tecniche Erboristiche-SISTE, aims at providing an in-depth analysis of the current regulatory situation of botanical products from a global perspective and the legal requirements that define their classification. Moreover, current approaches relevant to evaluation of the safety of such products in their pertinent regulatory frameworks will be discussed and clarified. State of the art activities of EFSA and EMEA in this field will be presented, to provide an updated insight. Recognised experts from academia, industry, and institutions will offer a range of viewpoints and will contribute, through interactive discussions, to highlight the future of this rapidly evolving sector.

I prodotti di origine vegetale vengono utilizzati con molteplici destinazioni di impiego, come alimenti, come farmaci e come rimedi erboristici, e ricadono perciò nell'ambito di classificazioni e normative diverse.
Questo convegno, promosso da NFI- Nutrition Foundation of Italy, ASSOERBE, SIAR - Società Italiana Attività Regolatorie, e SISTE - Società Italiana delle Scienze e delle Tecniche Erboristiche, intende offrire un'approfondita analisi della situazione regolatoria attuale di questi prodotti. Verranno discussi e chiariti i criteri applicati alla valutazione della loro sicurezza, considerandone l'inquadramento regolatorio pertinente; verrà inoltre presentato un aggiornamento delle attività di EFSA e di EMEA in questo campo ed esperti qualificati dell'università, dell'accademia, dell'industria e delle istituzioni offriranno un ampio ventaglio di punti di vista per delineare, attraverso discussioni interattive, le prospettive future di un settore in fase di rapida evoluzione.

GENERAL INFORMATION

Simultaneous Translation
The official languages of the meeting will be Italian and English. A simultaneous translation from Italian into English (and viceversa) will be provided. Earphones for simultaneous interpretation will be delivered at the Simultaneous translation desk on the second floor of the Congress Centre only to participants regularly registered against release of a personal identification document. Such personal document will be given back when the earphone is returned.

Conference Secretariat
The Secretariat will open at 8.45 a.m. and close at 6.00 p.m. on November 20, 2008. The following services are available at the secretariat desk:

- Registration
- Secretariat
- Information

Registration and Fees
Participants are entitled to:
- attend the scientific sessions
- receive the conference material;
- nr. 1 lunch and nr. 2 Coffee breaks;
- CD Rom of the speakers' slides (to be delivered after the Conference)

On-site Registration Fees
- for members of ASSOERBE - SIAR – SISTE **€ 360,00** (€ 300,00+ VAT 20%)
- for non members **€ 420,00** (€ 350,00+ VAT 20%)

Payments by cash on your arrival at the conference site.

Badges
Admission to the scientific sessions is reserved only to regularly registered participants; they are kindly requested to wear the conference badge.

Certificate of attendance
Certificate of attendance will be available on request at the end of the Conference at the Secretariat desk. The requested form is enclosed in the conference bag.

Participants are requested to refrain from smoking and switch off their mobile phone in the meeting area.

INFORMAZIONI GENERALI

Traduzione Simultanea
Le lingue ufficiali del Convegno sono l'italiano e l'inglese. È prevista la traduzione simultanea italiano-inglese e inglese-italiano. Le cuffie per la traduzione simultanea saranno distribuite al secondo piano del Centro Congressi soltanto ai partecipanti regolarmente iscritti, ai quali verrà richiesto di consegnare un documento di identità. Il documento verrà restituito a riconsegna della cuffia.

Segreteria Congressuale
La Segreteria Congressuale sarà a disposizione dei partecipanti a partire dalle ore 8.45 fino alle ore 18.00 di giovedì 20 novembre. Il personale sarà a disposizione per distribuire ai partecipanti il materiale congressuale, registrare nuove iscrizioni e fornire informazioni.

Quote di iscrizione
La regolare iscrizione al Convegno comprende:
- Partecipazione alle sessioni scientifiche;
- Materiale congressuale;
- Nr. 1 colazione di lavoro e 2 Coffee break;

Il CD rom delle diapositive dei relatori verrà inviato dopo il Convegno

Quote di iscrizione on-site:
- per associati a ASSOERBE - SIAR – SISTE **€ 360,00** (€ 300,00+ IVA20%)
- per i non soci **€ 420,00** (€ 350,00+ IVA 20%)

Il pagamento della quota potrà essere effettuato in contanti o tramite assegno bancario o circolare intestato a Centro Studi dell'Alimentazione.

Badge
A tutti gli iscritti verrà consegnato un badge nominale da esibire, per poter accedere alle sessioni scientifiche.

Certificato di partecipazione
Su richiesta, il certificato di partecipazione sarà a disposizione dei partecipanti presso la Segreteria alla fine del Convegno. Il modulo di richiesta è inserito nella borsa congressuale.

Si informa che nel Centro Congressi è vietato fumare.
Si raccomanda vivamente di spegnere il cellulare prima di entrare in sala.

PROGRAMME

hour		*Abstract page ref.*
9,30	**Introductory remarks** **Rodolfo PAOLETTI** **Vittorio SILANO**	– –
9,40	**I session** **The regulatory framework** *Chair:* **Giuseppe RUOCCO** European and national regulations relevant to botanical products **Barbara KLAUS**	17
10,00	**II session** **Activities of EFSA and EMEA** *Chair:* **Agostino MACRI'** Activities of EFSA **Bernard BOTTEX** Activities of HMPC/EMEA **Lucia D'APOTE** *Discussant:* **Gioacchino CALAPAI**	25 27
10,50	*Coffee Break*	

PROGRAMMA

ora		*Abstract a pagina:*
9,30	**Note introduttive** **Rodolfo PAOLETTI** **Vittorio SILANO**	– –
9,40	**I sessione** **Il contesto del mercato e le normative applicabili** *Moderatore:* **Giuseppe RUOCCO** Le normative applicabili nell'Unione Europea **Barbara KLAUS**	17
10,00	**II sessione** **Attività dell'EFSA e dell'EMEA** *Moderatore:* **Agostino MACRI'** Attività dell'EFSA **Bernard BOTTEX** Attività di HMPC/EMEA **Lucia D'APOTE** *Discussant:* **Gioacchino CALAPAI**	25 27
10,50	*Coffee Break*	

11,10

III Session
Analysis of the implementation of regulations on food supplements and traditional herbal medicines in the UE member states

Chair: **Alessandro TORSELLO**

Viewpoints of industry associations

Viewpoints of the institutions

Discussant: **Giuseppe RUOCCO**

12,35 *Lunch*

11,10

III sessione
Analisi dell'attuazione delle normative relative a integratori alimentari e medicinali tradizionali negli Stati Membri dell'UE

Moderatore: **Alessandro TORSELLO**

Il punto di vista delle Associazioni delle Aziende del Settore

Il punto di vista delle Istituzioni

Discussant: **Giuseppe RUOCCO**

12,35 *Colazione di Lavoro*

13,30 **IV session**
Round Table: The way forward

Chair: **Vittorio SILANO**

Participants:
Bernard BOTTEX
Hubertus CRANZ
Lucia D'APOTE
Marisa DELBO'
Agostino MACRI'
Luisella MAJORI
Valentino MERCATI
Anna PAONESSA
Bruno SCARPA
Hartwig SIEVERS
Marinella TROVATO

15,30 **Final discussion**

16,00 *Coffee break*

16,15 **V session**
Issues related to traditional Chinese Medicine

Chair: **Alvaro VACCARELLA**

17,30 *End of the Conference*

13,30 **IV sessione**
Tavola Rotonda: Sviluppi futuri

Moderatore: **Vittorio SILANO**

Partecipanti:
Bernard BOTTEX
Hubertus CRANZ
Lucia D'APOTE
Marisa DELBO'
Agostino MACRI'
Luisella MAJORI
Valentino MERCATI
Anna PAONESSA
Bruno SCARPA
Hartwig SIEVERS
Marinella TROVATO

15,30 **Discussione finale**

16,00 *Coffee break*

16,15 **V sessione**
Aspetti Connessi alla medicina tradizionale cinese

Moderatore: **Alvaro VACCARELLA**

17,30 *Fine del Convegno*

SPEAKERS AND CHAIRMEN

Bernard BOTTEX - Scientific Officer, Unit of the Scientific Committee & Advisory Forum, European Food Safety Authority - EFSA (Parma, Italy)

Gioacchino CALAPAI - Department of Clinical and Experimental Medicine and Pharmacology, University of Messina (Messina, Italy)

Maria Laura COLOMBO – Dept. Drug and Science Technology, School of Pharmacy, University of Torino (Turin, Italy)

Ario CONTI - Alpine Institute of Chemistry and Toxicology, Alpine Foundation for Life Sciences (Olivone, Switzerland)

Patrick COPPENS - Secretary General, Botanical Forum (Bruxelles, Belgium)

Hubertus CRANZ - Director - General, Association of the European Self-Medication Industry - AESGP (Bruxelles, Belgium)

Lucia D'APOTE - Post-Authorisation Evaluation of Medicines for Human Use Unit, Regulatory Affairs and Organisational Support (RAOS) Sector, European Medicines Agency - EMEA (London, UK)

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Anna PAONESSA – Italian Association of Food Product Industries - AIIPA (Milan, Italy)

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Marinella TROVATO - President, Società Italiana delle Scienze e delle Tecniche Erboristiche - SISTE (Milan, Italy)

Alvaro VACCARELLA - Scientific and Medical Office, China-Italy Foundation (Milan, Italy)

Franco VINCIERI – Department of Pharmaceutical Sciences, University of Florence (Florence, Italy)

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Valentino MERCATI - Vice Presidente ASSOERBE (Milano)

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Bruno SCARPA - D.G. Sicurezza degli Alimenti e Nutrizione, Dipartimento Sanità Pubblica Veterinaria, Nutrizione e Sicurezza degli Alimenti, Ministero del Lavoro, della Salute e delle Politiche Sociali (Roma)

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Alvaro VACCARELLA - Scientific and Medical Office, China-Italy Foundation (Milano)

Franco VINCIERI - Dipartimento di Scienze Farmacologiche, Università degli Studi di Firenze (Firenze)

INVITED SPEAKERS' ABSTRACTS

ABSTRACT DEI RELATORI

European and National regulations relevant to Botanical Products - The Regulatory framework

Barbara KLAUS
Lawyer, meyer//meisterernst (Milan, Italy); Lecturer in food law (University of Munich and European Centre for Judges and Lawyers in Luxemburg)

I. Introduction

With the advent of introducing new segments such as functional foods, herbal medicines and cosmetic pharmaceuticals, we are becoming aware that the marketing of botanical products is becoming more and more economically important; as these products are widely marketed at a national, European and International level. Examples include ginkgo, garlic, ginseng, aloe vera, rosemary extracts etc. In view of the increasing over the border marketing of these products, questions regarding the regulatory framework for botanicals are arising, especially among economic operators and authorities.
Particularly, there are some general concerns with respect to botanicals and botanical preparations mainly relating to quality and safety issues. Furthermore, the "*heterogeneous group*" of botanicals includes products which, mainly depending on their intended uses and presentations, fall under many different Community regulatory frameworks and for some types of products, the legal provisions for a preliminary risk assessment, do not exist at this time. In the following information, an overview is given regarding these regulatory aspects concerning these botanicals.

II. Delimitation between foodstuffs, cosmetics and medicinal products

First of all, it is important to bear in mind that 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) may be used for many different scopes; and in particular in the manufacture of foodstuffs, of cosmetics and of medicinal products. As foodstuffs, cosmetics and medicinal products are subject to **different** regulatory frameworks; from a juridical point of view, it is therefore very important to first of all clarify, in each single case, whether the botanical in question is to be qualified as a foodstuff, a cosmetic product **or** a medicinal product.
The legal definitions of the above products have been taken into an account at a Community level. A **medicinal product** is any combination of substances (or a single substance) 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 medical diagnosis (medicinal product by function) or any (combination of) substance presented as having properties for treating or preventing disease in a human being's metabolic action, or to making a medical diagnosis, which is in reference to a medicinal product delivered through a presentation.
A **cosmetic product** is any substance or preparation (including botanicals) intended to be placed in contact with the various external parts of the human body or with the teeth and the mucous membranes of the oral cavity, with a view used exclusively to cleaning them, perfuming them, changing their appearance, and/or correcting body odours, and/or protecting them or keeping them in a so called, good condition. A **foodstuff** is any substance, whether it is partially processed, processed or unprocessed which is intended to be, or reasonably expected to be ingested by humans, **including** drinks, chewing gum, and any substance (including water), intentionally incorporated into the food during its manufacture, preparation or treatment. However, **food** shall **not include**: Feed, live animals (unless they are prepared for marketing for human consumption, e.g. oyster), plants prior to harvesting, **medicinal products**, residues and contaminants, **cosmetics**, tobacco and tobacco products, narcotic or psychotropic substances.
According to the jurisprudence of the Court of Justice in Luxembourg, the determination

as to whether a product falls within the definition of a medicinal product, a foodstuff or a cosmetic product must be based solely on a **case by case basis**, taking into account all of the characteristics of the product, in particular its composition, its pharmacological properties to the extent in which they can be established in the present state of scientific knowledge; the manner in which it is used, through to the extent of its distribution, and lastly through its familiarity to consumers and the risks which its use may entail (see amongst others EJC Judgment of 21 March 1991, *Jean-Marie Delattre*, in Case C-369/88; and of 15 November 2007, *Commission/Germany*, in case C-319/05). The Law on medicinal products (see Art. 2, para 2 of Directive 2001/83/EC which has been transposed into the Italian Law by the Decreto Legislativo 24 April 2006, No 219), provides that in **cases of doubt**, where, taking into account all its characteristics, a product may fall within the definition of a "*medicinal product*" **and** within the definition of a product covered by other Community legislation (e.g. foodstuff or cosmetic products), the provisions regarding **medicinal products** shall apply.
Thus the legal concepts of foodstuffs, cosmetics and medicinal products are then brought into balance at a Community level; throughout the Law practise it occurs that national authorities qualify one and the same (botanical) product as a medicinal product in one Member State and as a foodstuff (or as a cosmetic product) in another Member State; this creates further barriers which will disturb the flow of the trade.

III. Medicinal Products

Herbal medicine, that use plants (whole, fragmented or cut, plants or preparations obtained by subjecting herbal substances to treatments such as through extraction, distillation, expression, fractional, purification, concentration or fermentation) as these remedies have been used around the world for centuries; and is still the most widely practised form of medicine right across the planet. Moreover, it shall be born in mind that also many conventional medicines have originated from a single active ingredient of plant material.

Principally, medicinal products, including herbal drugs, may only be placed on the market of a Member State in the European Union unless an **authorisation** has been issued by the competent authorities of that Member State or by the European Medicines Agency (London). To receive a marketing authorisation, (herbal) medicines are required to meet all safety, quality and efficacy criteria. Thus, applications for authorisation need to be accompanied by a dossier containing particulars and documents relating to the results of physico-chemical, biological or microbiological tests as well as pharmacological and toxicological tests and clinical trials carried out on the product and thus proving its quality, safety and efficacy.
However, applicants are not obliged to provide the results of toxicological or pharmacological tests or clinical trials, if they can demonstrate that the active substances (e.g. botanicals) of the medicinal product have been used through a **well established medicinal use** in the Community for at least ten years, also complying with an acceptable level of safety (abridged applications). Many well established medicines were originally derived from plant materials.
For those (herbal) medicinal products which, despite their long tradition, do not fulfill these requirements of a well-established medicinal use; considering however, the particular characteristics of these medicinal products (especially their long standing tradition), a simplified **registration procedure** was established at a Community level for **traditional herbal medicinal products** for human use under Directive 2004/24/EC. The normal requirement for medicines to be proven to be efficacious, as required under Directive 2001/83/EC, which is replaced by a requirement to demonstrate 30 years of traditional use for the required medicinal indication. Under the aforementioned Directive, also the **Committee on Herbal Medicinal Products** (HMPC) has been established; whose main task is to set up Community herbal monographs and entries to the "*List of herbal substances, preparations and combinations thereof for use in traditional medicinal products*". This list shall contain, for each herbal substance or preparation, the indication,

the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance, or preparation used as an ingredient of a traditional medicinal product. Furthermore, the Committee has issued a number of procedural and regulatory documents, as well as scientific guidelines (all available on Internet: http://www.emea.europa.eu/htms/human/hmpc/hmpcguide.htm) such as a "*Guideline on quality of herbal medicinal Products / traditional herbal medicinal products*" of 30 March 2006 and "*Guideline on the assessment of genotoxicity of herbal substances/preparations*" of 21 May 2008.

Finally, we introduce homeopathy and its sustainability of using plants materials as remedies. According to the Community code relating to medicinal products for human use, **homeopathic medicinal products** may be subject to a special, **simplified authorisation or registration procedure**, provided (a) they are administered orally or externally; (b) there is no specific therapeutic indication on the labelling of the medicinal product or in any information relating thereto; (c) and that there is a sufficient degree of dilution to guarantee the safety of the medicinal product.

As far as the **presentation of (herbal) medicinal products** is concerned, a number of specific particulars must appear on their outer packaging or, where there is none, the immediate packaging (including, for instance, the name of the medicinal product, its dose and pharmaceutical form; qualitative and quantitative composition in respect of active substances; method of administration; special warnings; etc.). There are specific limitations as to how the advertising is released to the general public through medicinal products; and the advertising techniques for some specific medicinal products are totally forbidden.

IV. Cosmetics

The Rules regarding the composition and the presentation of cosmetics have already been brought to our attention on a Community level; through Council Directive 76/768/EEC.

As far as the **composition** is concerned, cosmetics must not be harmful to human health when they are applied under normal or foreseeable conditions of use. The aforementioned Directive sets out a list of substances which cannot be included in the composition of cosmetic products (negative list; see Annex II; for example *Atropa belladonna, Hyoscyamus niger L., Physostigma venenosum Balf.*) and a list of all substances which is instilled in cosmetic products, may only be contained under the restrictions and conditions laid down (Annex III; for example *Oak moss extract, Abies alba needle oil and extract*). Moreover, the Cosmetics Directive also contains lists of colourings (Annex IV), preservatives (Annex VI) and UV filters (Annex VII) permitted in cosmetic products.

As far as the **labelling** is concerned, containers and/or packaging must bear specific indications (e.g. name or trade name and address or registered office of the manufacturer or of the person responsible for marketing the cosmetic product within the Community; all ingredients, precautions for use; product function, etc.). Moreover, labelling and **advertisement** of cosmetics must not be misleading (for instance, it must not imply that these products have characteristics which they do not have; all claims regarding the effects of certain cosmetics must only be based on scientific evidence).

V. Foodstuffs

Botanicals and botanical preparations are widely used in food manufacturing, especially in **food supplements** and in **enriched foodstuffs**. The manufacturing and marketing of these categories of foodstuffs has only partially been harmonised at EU level up to this point: Directive 2002/46/EC on food supplements and Regulation (EC) No 1925/2006, that have been laid down by specific common rules regarding the labelling, presentation and advertising of food supplements and enriched foodstuffs in general; as well as rules for vitamins and minerals used as ingredients in these foodstuffs supplements. Therefore there are no specific rules that have been laid down by Community Law for **other** nutrients than vitamins and minerals or substances with a nutritional or physiological effect, such as botanicals.

Directive 2002/46/EC foresees, that specific rules concerning these other substances used

as ingredients of food supplements should be laid down at a later stage, provided that adequate and appropriate scientific data regarding them, become freely available. So far, no such regulatory Rules have been elaborated on a Community level. Furthermore, Regulation (EC) No 1925/2006 gives the possibility to put under scrutiny and if necessary, to restrict the use of substances such as botanicals added to foods or used in the manufacture of foods under conditions that would result in the ingestion of amounts greatly exceeding those reasonably expected to be ingested under normal conditions of consumption of a balanced and varied diet and/or would otherwise represent a potential risk to consumers. Up until this time, there are no such restrictions that have been adopted on a Community Level.

The use of botanicals and botanical preparations in food is regulated under the General Food Law (178/2002/EC), which assigns the primary legal responsibility for the safety of the products placed on the market to business operators. The Regulation however does not provide any guidance on how the safety of these products should be assessed. Thus the use of botanicals in foodstuffs is still regulated throughout the Member States by differing national rules. As a conseguence, as the use of botanicals in food supplements and enriched foodstuffs are not yet completely regulated by specific Community Laws, the **principle of mutual recognition** is still applicable. According to this concept, a product (e.g. a foodstuff) which is lawfully manufactured and/or marketed in one Member State must be accepted in the other Member States even though it is not in line with the domestic rules (e.g. technical rules regarding the composition). Only in certain circumstances when it is necessary to satisfy mandatory requirements (e.g. protection of public health and consumer rights) that the Member States may forbid the marketing of those imported products, provided that they do not guarantee an equivalent level of protection.

Nevertheless, problems have arisen in this regard; as specific botanicals were evaluated by some Member States as safe and by some other Member States as unsafe; this different approach impedes the free movement of foodstuffs containing certain botanicals and once again creates an inordinate barrier towards the trade. In order for us to eliminate those barriers, the European Food Safety Authority, in 2005, initiated the work for a science-based guidance team for assessing the safety of botanicals; in order to evaluate - with a science-based approach - the food safety aspects and a description of the information that should be taken into account to establish the safe use of the botanical or botanical preparation. In June 2008 **EFSA** published an updated **guidance document** on the **safety assessment of botanicals and botanical preparations.**

Furthermore, it must be born in mind that also relevant in the context of the use of botanicals in foodstuffs are the Directives 1989/398/EEC on food for special purposes and the Regulation (EC) No 1997/258 on "***Novel Foods***" (which are for specific foods and ingredients that were not onmarket before May, 1997 and cannot demonstrate a safe history either) that provide additional channels for some botanicals and botanical preparations to enter the food market; for instance, recently, Baobab dried fruit pulp, refined echium oil and allanblackia seed oil have been approven as novel food ingredients.

Finally, as an increasing number of foods containing botanicals labelled and advertised in the Community bear **nutrition** (e.g. " *rich in green tea extract*") and **health claims** (e.g. "*rich in green tea extract which contributes to maintain a healthy cardiovascular*"), the Rules established by Regulation (EC) No 1924/2006 are relevant in this field; and shall be observed by the economic operator. According to this Community Law, any claim made on foods need to be clear, accurate, substantiated and authorized on a Community level; in order to enable consumers to make informed and meaningful choices when it comes to food and drinks.

Activities of EFSA

Bernard BOTTEX
Scientific Officer, Unit of the Scientific Committee & Advisory Forum, European Food Safety Authority - EFSA (Parma)

The purpose of the presentation is to update the participants on the current status of EFSA's activities related to the assessment of botanicals and botanical preparations used in food or as food supplement.

The presentation will first address the guidance being developed by the EFSA Scientific Committee for the safety assessment of botanicals and botanical preparations used as ingredients in food supplement; it will particularly focus on the testing phase of the proposed framework by an EFSA Scientific Cooperation (ESCO) Working Group composed of experts identified both by EFSA and the European Member States having an interest in this topic.

In addition, participants will be briefly updated on the ongoing work of the EFSA Panel on dietetic products, nutrition and allergies (NDA) related to the scientific substantiation of function health under article 13 of Regulation (EC) 1924/2006 with a focus on the botanical claims.

Activities of HMPC/EMEA

Lucia D'APOTE
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The presentation will provide an overall summary of the legislative framework for traditional herbal medicinal products (THMPs) and will outline the opportunities offered by the new legislation to register traditional and modern herbal medicinal products. In addition, the participants will be informed about the role of the Committee on Herbal Medicinal Products (HMPC) and its recent achievements working towards facilitating the access to the European market. A section of the presentation will focus on cooperation between EFSA and HMPC on assessment of safety aspects and borderline between herbal food supplements and herbal medicinal products.

THE CO-EXISTENCE OF BOTANICAL FOOD SUPPLEMENTS AND HERBAL MEDICINAL PRODUCTS

Patrick COPPENS
Secretary General, Botanical Forum (Bruxelles, Belgium)

Botanicals and botanical ingredients are used in a variety of products including foodstuffs, food supplements, cosmetics and medicinal products. The choice of the legal framework to apply lies with the manufacturer and is determined by the intended use of the product.

General provisions for botanical food supplements are harmonised by Directive 2002/46 on food supplements. No detailed harmonised rules exist for botanicals, so Member States' legislation applies, subject to the principle of mutual recognition.
Botanical ingredients used in medicines are covered by Medicinal law (Directive 2001/83/EC) and require a medicinal licence prior to marketing. A specific category is traditional herbal medicinal products, covered by Directive 2004/24/EC.
Thus, the EU legal framework intends that food supplements and medicinal products coexist, even if they are both presented in dose form and contain the same type of ingredients. The main difference is their intended use.

In some cases it may not be sufficiently clear if a product should fall under medicinal law or food law. In such cases article 2b of the medicinal product legislation may apply: "in cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provisions of the MPD shall apply". The scope of this provision is firmly limited to "cases of doubt" and is restricted to individual products.

The European Court of Justice (ECJ) has given clear indications on how to apply this through numerous court cases.
- The first one is that it is for the national authorities to determine whether a product falls within the definition of a medicine. Such judgements must be done on a case-by-case basis, taking account of all the characteristics of the product. Amongst these characteristics, the ECJ lists in particular the product's composition, its pharmacological properties to the extent to which they can be established in the present state of scientific knowledge, the manner in which it is used, the extent of its distribution, its familiarity to consumers and the risks which its use may entail.
- Secondly, the ECJ also indicates that a product must have a certain therapeutic effect before it can be considered medicinal. A physiological effect is not specific to medicinal products but is also among the criteria used for the definition of food supplements. Therefore, it is not sufficient that a product has properties beneficial to health in general; it should strictly speaking also have the function of treating or preventing disease.

This confirms the principle that no ingredient or group of ingredients as such can be judged to be "medicinal by function" without considering the end-products they are used in. A borderline case therefore cannot be solved in a general way based upon one of its ingredients, but only after a case-by-case assessment of the final product.

Herbal medicines in the European Union

Hubertus CRANZ

Director - General, Association of the European Self-Medication Industry - AESGP (Bruxelles, Belgium)

Back in 1998, AESGP carried out a study for the European Commission on the situation of herbal medicinal products in the European Union and made a number of recommendations how to improve the regulatory and legislative environment for such products in Europe.[1]

In 1999, the European Commission's directive on the well-established use was adopted, which clarified the legal and regulatory situation for those herbal medicines which can be part of the existing marketing authorisation system. Particular references were made to the necessary safety profile of such medicines. This was complemented in 2004 by a specific legal framework for herbal medicines based on traditional use with a plausible level of evidence. This directive clarified, among other issues, the composition, the acceptance of non-EU tradition as well as labelling and advertising requirements for such products. The same level of safety requirements as for herbal medicines of well-established use is kept for traditional herbal medicines.

In addition to the adjustments in legislation, the Committee on Herbal Medicinal Products (HMPC) was created at the European Medicines Agency. The establishment of monographs and list entries are key elements of the work of the HMPC.

On 29 September 2008, the European Commission adopted its report on the implications of the traditional herbal medicines directive, which shows:

- a relatively low number of applications
- considerable achievements of the HMPC in relation to monographs/preparation of list entries as well as guidelines related to herbal medicines
- uncertainties about the need for studies in relation to genotoxicity in the context of the adoption of monographs/list entries

The report suggests:

- to cover products with other substances, e.g. of animal, mineral or metallic origin and micro-organisms, with a similar legislative approach in the future
- not to change the scope of application concerning the route of administration, indications, minimum use in the Community

AESGP overall supports the conclusions given in the report. Emphasis in the near future should be on:

- the recognition of monographs as a basis for authorisations/registrations in all EU countries
- reasonable fee structure
- adequate implementation of the existing rules by keeping the better regulation principles in mind[2]

[1] http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc99/herbal_medecines_en.pdf

[2] http://www.aesgp.be/SmartRegulation/SmartRegulation2015.pdf

Normativa relativa a integratori alimentari e medicinali tradizionali negli stati membri dell'UE. Il punto di vista delle istituzioni: Settore Alimentare

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In attesa di specifiche disposizioni comunitarie programmate a seguito dell'emanazione della direttiva 89/398/CEE sui prodotti destinati ad una alimentazione particolare, a livello nazionale venivano classificati come integratori alimentari solo prodotti con valenza nutrizionale derivante da apporti predefiniti di sostanze nutritive (esempio vitamine e minerali).

Conseguentemente, i prodotti a base di sole piante privi nel contempo di finalità terapeutiche e di valenza nutrizionale, i cosiddetti prodotti erboristici, venivano forzatamente commercializzati alla stregua di preparati alimentari, in vista di un inquadramento specifico avviato a più riprese senza mai giungere a termine (nei disegni di legge succedutisi sulla materia sono state incluse la lista delle piante ammesse nei prodotti erboristici e la lista delle piante da commercializzare solo attraverso il canale delle farmacie per il particolare profilo di attività).

L'avvento della direttiva comunitaria 2002/46/CE ha risolto in modo del tutto logico e proporzionato una situazione così frazionata, parificando come integratori prodotti con nutrienti e/o sostanze non nutritive. Queste ultime, peraltro, sono state definite dal regolamento (CE) 1924/2006 come "sostanze di altro tipo", aventi comunque un effetto "nutrizionale o fisiologico", a conferma della impossibilità di demarcare concettualmente i costituenti degli alimenti tra nutrienti e sostanze non nutritive.

La descritta evoluzione ha avuto una forte influenza a livello nazionale per quanto concerne le piante impiegabili negli integratori.

Quelle comunemente utilizzate nei prodotti erboristici risultano ammesse in quanto tale collaudo fa venir meno la preventiva applicabilità del regolamento (CE) 258/97 sui novel food. Resta ferma ovviamente l'applicabilità di detto regolamento ai fini di un eventuale impiego come ingredienti di piante prive di storia di consumo significativo nell'UE.

Al momento, è in corso la compilazione della lista completa delle piante in uso negli integratori, che sarà pubblicata prossimamente sul portale del Ministero, dove è invece da tempo pubblicata la lista delle piante non ammesse, che riprende per la gran parte le piante a loro volta non ammesse nei prodotti erboristici.

Sul sito della Commissione UE è stato pubblicato di recente il "Catalogo" sui novel food, recante per un certo numero di sostanze, tra cui molte piante, lo "status" circa l'applicabilità o meno del regolamento (CE) 258/97 secondo quanto segnalato dai Paesi membri sulla sussistenza o meno della storia di consumo. La sigla "FS" indica che per l'impiego della sostanza o della pianta nel solo settore degli integratori il regolamento non si applica.

Per quanto riguarda i claims, ai sensi del citato regolamento (CE) 1924/2006 è stato trasmesso alla Commissione UE l'elenco di quelli impiegati a livello nazionale sui "botanicals".

In linea generale, fermo restando che a livello nazionale per immettere in commercio gli integratori occorre notificarne l'etichetta al Ministero, non vi sono preclusioni di partenza per l'impiego di una pianta se la stessa:

- è inclusa nell'elenco di quelle ammesse,

- è classificata come "FS" nel catalogo della Commissione UE,

- è presente in un integratore alimentare legalmente commercializzato in altri Stati membri.

Per una collocazione di prodotti a base di piante al di fuori degli integratori si passa direttamente nel settore dei medicinali, dove l'area borderline più prossima è quella dei medicinali vegetali tradizionali regolamentati dalla direttiva 2004/24/CE.

In relazione alle linee di demarcazione, il Ministero dovrà fornire specifiche indicazioni entro il 20 maggio 2010, secondo quanto è stato previsto dal decreto legislativo 24 aprile 2006, n. 219 "Attuazione alla direttiva 2001/83/CE e successive direttive di modifica" (tra cui, in particolare, la suddetta direttiva 2004/24/CE).

Normativa relativa a integratori alimentari e medicinali tradizionali negli Stati Membri dell'UE. Il punto di vista delle Istituzioni: Settore farmaceutico

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A seguito di specifica indagine effettuata, che ha evidenziato una profonda disparità all'interno degli Stati membri dell'Unione europea circa lo stato legale, le procedure e le disposizioni relative ai prodotti di origine vegetale, il Parlamento Europeo ed il Consiglio, su proposta della Commissione Europea, hanno emanato la direttiva 2004/24/CE al fine armonizzare le valutazioni a livello europeo e facilitare la registrazione di medicinali di origine vegetale (o fitoterapici), superando i problemi legati alla diversa interpretazione da parte degli Stati membri circa i requisiti di documentazione da presentare a supporto delle domande di autorizzazione su base bibliografica per i medicinali di "uso medicinale ben noto".
Con la medesima direttiva è stata istituita una nuova procedura speciale semplificata di registrazione per i medicinali di origine vegetale che sono usati tradizionalmente da lunga data e che non presentano una riconosciuta efficacia, ma hanno un livello accettabile di sicurezza e qualità analoga a quella degli altri medicinali di origine vegetale.
Tale strumento legislativo si prefigge di raggiungere il duplice scopo di garantire la tutela della salute pubblica, attraverso la definizione dei requisiti minimi di qualità, sicurezza ed efficacia dei fitoterapici tradizionali e di facilitare gli scambi nel settore dei medicinali tradizionali all'interno della Comunità senza comportare discriminazioni e distorsioni della concorrenza tra i fabbricanti di questi prodotti.
La direttiva 2004/24/CE è stata recepita in Italia nel D. L.vo 219 del 24 aprile 2006, che rappresenta la codifica della legislazione farmaceutica italiana; pertanto anche in Italia è applicabile la procedura speciale per la registrazione dei medicinali tradizionali di origine vegetale (o fitoterapici tradizionali) ed è previsto che entro il 20 maggio 2011 tutti i fitoterapici tradizionali in commercio debbano essere soggetti a quanto stabilito dalla nuova normativa.
Per consentirne la piena applicazione nei termini previsti, secondo il disposto dell'art. 27, comma 5 del D.L.vo 219/06, il Ministero della salute dovrà emanare, entro il 20 maggio 2010, specifiche indicazioni volte a chiarire la linea di demarcazione fra la disciplina dei medicinali di origine vegetale e quella degli alimenti o di altri prodotti oggetto di normativa comunitaria (dispositivi medici, supplementi alimentari e cosmetici), anche sulla base degli orientamenti assunti in materia dalla Commissione Europea e dalla Corte di giustizia.
Nel corso della presentazione sarà illustrato lo stato di applicazione della direttiva in Italia e negli Stati Membri con riferimento all'esperienza finora acquisita.
Sarà anche illustrato il contributo dell'Italia ai lavori del Comitato per i medicinali di origine vegetale (HMPC), alla redazione delle "**monografie comunitarie sulle piante e loro preparazioni**", che costituiscono la base bibliografica per le autorizzazioni dei medicinali di "impiego medico ben noto" e di "impiego tradizionale", alla predisposizione dell'"**elenco di sostanze vegetali, preparazioni vegetali e loro associazioni da usare nei medicinali vegetali tradizionali**", nonché allo sviluppo delle **linee guida** utili alla predisposizione dei dossier di registrazione.

SETTORE DEI PRODOTTI VEGETALI NON INDUSTRIALI

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La preparazione in farmacia trova la sua piena giustificazione quando risponde ad esigenze di personalizzazione della terapia con sufficienti garanzie di qualità per il consumatore, ovvero quando consente al paziente di disporre del medicinale idoneo nel caso in cui l'industria farmaceutica non sia in grado di soddisfare una sua particolare esigenza. Le motivazioni principali riguardano la personalizzazione del dosaggio, la necessità terapeutica di principi attivi difficilmente o non più reperibili, l'instabilità del medicinale, ed inoltre la possibilità di associare più principi attivi, di variare la forma farmaceutica o gli eccipienti rispetto al prodotto commercializzato. È comunque indispensabile che ogni medicinale allestito risponda a precisi requisiti in termini di qualità, efficacia e sicurezza, nel rispetto dell'evoluzione scientifica e tecnologica e quindi secondo lo stato dell'arte.

L'Unione Europea definisce "formula magistrale" i medicinali preparati in farmacia in base ad una prescrizione medica destinata ad un determinato paziente e "formula officinale" i medicinali preparati in farmacia in base alle indicazioni di una farmacopea e destinati ad essere forniti direttamente ai pazienti che si servono in tale farmacia (direttiva 2001/83/CE e succ. mod., recepita con il D.L.vo n. 219/06). La normativa nazionale (legge 94/98) vincola il medico all'utilizzo di principi attivi noti alla pubblica Amministrazione, e quindi egli può prescrivere medicinali contenenti principi attivi descritti nelle farmacopee dei Paesi dell'Unione europea o contenuti in medicinali prodotti industrialmente di cui è autorizzato il commercio in uno stato membro (anche qualora l'AIC sia stata revocata o non confermata per motivi non attinenti ai rischi di impiego del principio attivo). Il medico può anche utilizzare sostanze contenute in prodotti non farmaceutici per uso orale o in cosmetici regolarmente in commercio nell'UE, nel caso, rispettivamente, di preparazioni per uso orale o per uso esterno.

Tradizionalmente la farmacia ha sempre trattato i prodotti di origine vegetale e questa peculiarità è riconosciuta dal legislatore.
I derivati di origine vegetale possono essere utilizzati quali principi attivi di medicinali, la stessa farmacopea (FU XI ed.) riporta le monografie di droghe vegetali, estratti, infusi e decotti, oli grassi vegetali, piante per tisane e preparazioni a base di droghe vegetali e, inoltre, nelle Norme di Buona Preparazione definisce dettagliatamente i requisiti di fornitura e di etichettatura delle materie prime di origine vegetale.
La farmacia è anche luogo privilegiato per la vendita di prodotti ad attività salutare. Sulla base di queste considerazioni il Ministero della salute ha confermato la possibilità per il farmacista di allestire anche prodotti di origine vegetale ad attività salutare nel rispetto delle Norme di Buona Preparazione.

New herbal compound against Alzheimer's disease from traditional medicine: huperzine

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Drug discovery from plants involves a multidisciplinary approach combining botanical, ethnobotanical, phytochemical and biological techniques. Plants continue to provide us new chemical entities (lead molecules) for the development of drugs against various pharmacological targets, including cancer, HIV/AIDS, malaria, Alzheimer's disease and pain. Several natural product drugs of plant origin are in clinical use, including paclitaxel, camptothecin-derived analogues, artemether, galanthamine to name a few, and some are undergoing Phase II and Phase III clinical trials.

Alzheimer's disease is currently thought to contribute to about 75% of all cases of senile dementia that occur in the U.S. The disorder is marked by reduced levels of acetylcholine, development of amyloid plaques, and degeneration of brain tissue. It produces cognitive and coordinative dysfunctions with notable loss of memory. From the modern medical viewpoint, the cause of Alzheimer's disease is not yet established.

Currently, there are two treatment approaches to Alzheimer's disease in China: use of complex herbal formulas based on the traditional methods of traditional Chinese medicine and containing Huperzia serrata microphyllus leaves, or administration of the alkaloid drug, huperzine, obtained from the plant.

Huperzia serrata (Thunb.) Trev. (syn. Lycopodium serratum Thunb.) is a non-flowering plant, it is a Chinese club moss plant. Huperzine, an anticholinesterase alkaloid produced by Huperzia plant, has two different structures, huperzine A and huperzine B, which have similar effects but differing activity levels (huperzine A being about 10 times as strong as huperzine B).

Historically, huperzine A has been used for the treatment of bruises, strains, swelling, schizophrenia, and fevers. Huperzine A was first isolated from the Chinese herb Lycopodium serratum in 1980 at the Zhejiang Academy of Medical Sciences and the Shanghai Institute of Materia Medica of the Chinese Academy of Sciences. Huperzine B was isolated five years later. The plant source, originally called Qian Ceng Ta, meaning thousand-layers pagoda (referring to the tall multi-leafed appearance of the plant), is also known in China as Jin Bu Huan, a term meaning "more valuable than gold," usually applied to plants that have potent analgesic actions.

The huperzine structure is different from other alkaloids isolated from club mosses, though systematic investigations of Chinese club mosses have found huperzine A in numerous species. The yield of huperzine A from H. serrata is reported to be about 0.1% on a dry weight basis.

This drug inhibits the breakdown of the neurotransmitter acetylcholine, allowing more of it available for brain functions, including memory. Huperzine A, a specific reversible inhibitor of acetylcholinesterase, is active at low nanomolar concentrations. This is the same mechanism of action of pharmaceutical drugs such as galanthamine (an alkaloid from Galanthus nivalis L. plant) used to threat Alzheimer's disease. Huperzine A has passed Phase II trials in the U.S. (Clinical Trials Identifier NCT00083590) and it may become available as a prescription drug at the end of this decade. These finding led to human trials and the subsequent marketing of the huperzine A as a treatment for Alzheimer's disease and related conditions.

Huperzine is also sold as a "brain booster" for enhancing memory and mental function in people without Alzheimer's disease. It is regulated as an herbal supplement in the U.S. and several firms required premarket notifications with the FDA for huperzine A products manufactured in China from natural sources. It is noteworthy that the marketing of a pure pharmaceutical compound as a food supplement raises important questions about the safety of natural remedies.

Flashes on Chinese Herb Medicine, new drugs research and occidental culture: might psychoneuroimmunomodulation bridge the gap between different cultures?

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Science and art need not to be in conflict: both require the use of imagination, cognitive insight, discipline, and creative application. During the last decades, conceptual shifts in biological sciences provided new evidence to support intuitive beliefs regarding the connection between the mind-body unit, external and/or internal stimuli such as viruses and bacteria, and primordial environmental stimuli such as the light : dark cycle, moon cycle, tides, magnetic forces, and humidity. Moreover, many new factors such as climate changes, air pollution, the rise in world population, particularly in developing countries, the rise of poverty in developed countries, and their social and environmental effects are becoming increasingly sophisticated. Consequently, the role of human management of the ecosystem has begun to be reconsidered by each and every one of us, scientists, politicians, and the lay public. On the other hand, methodological communication was not a major problem during the early days of medicine. Moreover, treatment modalities were based on a gift from Mother Nature: the plants and extracts thereof. Herbal medicines, which has to be integrated in this vision, has long been accepted treatment of various diseases in European countries, South/North America, Africa, Australia and Asia which includes China, the new emergent country. The traditional experience of Chinese herb has been highly treasured by the Chinese people as a very precious cultural heritage, and is plays an important role in the people's health service. It serves as the fundamental basis for drug research and the search for new drugs in modern China. Chinese herb medicines are all derived from natural products: both in the past and in the present, China is one of the leading nations in the use of drugs from natural origin. In comparison with as happened in occidental countries, as in Europe and or United States, Chinese herb medicine, whether in respect to production, application, or scientific research, has an equally important position in comparison with synthetic drugs and antibiotics. Apparently it could be difficult for occidental community, scientists, doctors, pharmaceutical companies understand this position because the different approach in studying medicinal plants, their products (natural and/or synthesis derived products similar to naturals) and each effective, or potential, therapeutic approach to cope diseases and disturbances. I would like to try to focalise on certain aspects of the Chinese medicine, to search a common point of view between two different philosophies of life: the occidental and the oriental one. I'm aware about the complexity of this matter and it is not easer to perform such analysis in a very short time. In the first part of this paper a brief introduction has been given along with limited examples of the development of Chinese traditional medicine, ancient medical literature, effective and secret prescriptions, principle of treatment, the incidental effect of drugs or plants acting upon the human body, and drugs used by the national minorities. China has a longer history in the use of herb medicines if compared with our countries and, thus, has accumulated a vast experience which frequently has demonstrated conspicuous and unique effects on certain diseases. Since the subject of traditional Chinese herb medicine is vast, I can only give a general out line. On the other hand in Europe, before 19th centuries phytomedicine was considered a scientific medicine and later, with the development of clinical chemistry, followed by many new developments based e.g. on biomedical engineering, physic and molecular medicine, new avenues of medical research were paved. These developments had their own powerful way, leaving phytomedicine separated, and one might argue that during this period between 1900 century and 2000

century, phytomedicine, in Europe and United States, was not considered a scientific medicine. Beside the groups that keep traditional medicine (including phytomedicine) alive, there were more and more scientists of modern education that found interesting aspect in studying the traditional discipline by use of the most recent methodology: chemical formulas and details about molecules that are fundamental for both modern phyto- and scientific medicine but also for a development of Oriental (Chinese) and Occidental (Europe) medical culture. In the last two decades researchers have published in peer reviewed journals, thus initiating the way to bring together these medical disciplines that in Occidental countries were separated for such long time, while in China were separated just from the high technologies. How it might be possible to lies Chinese and Occidental medicinal plant medicines, what progress has been and will be made in the next future? I believe that one model could be represented by Neuroimmuno-modulation. In 1987 in Dubrownik, N.H. Spector named a new discipline Neuroimmunomodulation. Later R. Ader called this disciple Psychoneuroimmunomodulation when the major emphasis was on its beha-vioural aspects. This new- old discipline is devoted to the study of the interaction at different morphologic and functional levels among the immune, nervous and endocrine systems. In fact, this science is the modern manifestation of an old science: "Neuroimmunomodulation is a modern reflection in neurosciences and immunosciences of the ideas and experience of philosophers and ingenious observers of ancient Egypt, Greece, China, India and other civilizations that the mind is involved in the defence against diseases. Twenty years ago neuroimmunomodulation was regarded by many conventional scientists almost as a form of witchcraft. Today, including medicinal plants, it may be one of the fastest growing areas of biomedical research in the world. Important clinical application will not be far behind. Relation between phytomedicines and neuroimmunomodulation, spanning immunology, neurobiology, neuroendocrinology, and behaviorral sciences, is growing and are currently in progress to discover new ways to treat various diseases, including for example, cancer, asthma, hypertension, arthritis, skin diseases, rheumatic diseases, cardiovascular and cerebrovascular diseases, to cope bacteria, parasites and viruses. Complexes interactions among the nervous, endocrine, and immune system have been investigated from the sub-cellular to the behavioural levels, using the modern tools of receptors and membrane physiology, biochemistry, pharmacology, immunology, chronobiology, and genetics. Moreover, scientists working in basic research have also become interested in establishing connections between psychoneuroendocrine immune interactions and exogenous therapeutic intervention with medicinal plants. In fact, a critical analysis reveals that the vast scientific literature on the relationship between medicinal plants, immune system, clinical studies, selected between European, Chinese and United States, is so heterogeneous that it seriously challenges the observer's capacity to find any order at all among these studies. With my talk I just offer my opinion as scientist with a long experience in neuroimmunomodulation research and a little shorter one in medicinal plants. I offer just one simple question: *Flashes on Chinese herb medicine, new drugs research and occidental culture: might psychoneuroimmunomodulation bridge the gap between different cultures?* I also hope to stimulate basic scientist, clinicians and pharmaceutical companies as partners in this beautiful and promising field of basic and applied research.

Traditional Chinese Medicine Herbal Drug Monographs in European Pharmacopoeia

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The introduction of Traditional Chinese Medicine herbal drug monographs into the European Pharmacopoeia was already long underway from both Herbal Drug Working Groups 13A and 13B. In 2007 the European Pharmacopoeia established a specific TCM-Herbals Working Party (TCM-HWP), constituted by experts from different countries of the European Community, having as exclusive task the compilation of monographs of the TCM herbal drugs. This TCM-HWP, whose first session took place in January 2008, will consider the work previously initiated by the Groups 13A and 13B to complete and finalize the monographs. Moreover, based on the present monographs of the Pharmacopoeia of the People's Republic of China, TCM-HWP will proceed to the compilation of the monographs of the most important TCM herbal drugs. The Chinese monographs have to be first carefully evaluated from a scientific point of view and then modified according to the requirements and style of the European Pharmacopoeia. Several problems encountered during this first phase of work will be presented.

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