Global Views 结合医学概览

The European directive on traditional herbal medicinal products: friend or foe for plant-based therapies?

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The European Parliament and Council enacted a directive on traditional herbal medicinal products (THMPD; Directive 2004/24/EC) as an amendment to an earlier directive on the use of medicinal products (Directive 2001/83/EC) on March 31st, 2004[1,2]. Since April 30th, 2011, all herbal medicinal products have to be produced under Good Manufacturing Practice (GMP) rules to fulfill quality and safety measures. In the present overview, we introduce the legal basis for herbal medicines and food supplements to the readers. The pros and cons are discussed and possible future perspectives are shown.

1 Regulation of traditional herbal medicinal products by the European community

As there was no Europe-wide but only individual national regulation procedures on herbal products, a regulatory approval process was launched for herbal products. The main topic of this directive is that all herbal medicinal products not approved before April 30th, 2004 need legal authorization to be marketed within European Union (EU). A transition period was set until April 30th, 2011, in which the marketing of such products can still be continued without official authorization to give further time for producers of herbal remedies to obtain approval. After this deadline, all herbal medicinal products have to be produced under GMP rules to fulfill the quality and safety measures. Exceptions from THMPD are herbal medicines that are produced on an individual basis, such as for patients after consultation of a medical doctor or herbalist. These individual remedies do not require licensing prior to their sale. The authorization process in comparison to other medications, for example, synthetic drugs, was simplified for those herbal medicines that are already used within the EU for 30 years or more or within the EU for 15 years and 30 years outside the EU. THMPD is also applied for herbal medicines for oral or topical use or for inhalation. Herbal products for intra-

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venous administration will not be authorized in general. Ancillary vitamins or minerals are allowed to be added to herbal medicines, but isolated plant constituents are not regarded as herbal medicines and THMPD is not applicable for these substances. They need full authorization as synthetic drugs.

In addition to Directives 2001/83/EC and 2004/24/EC, a number of recommendations have been published by the Medicines and Healthcare products Regulatory Agency (MHRA) to facilitate operating within the herbal medicine sector, for example, Guidance for Retailers, Wholesalers, Importers and Manufacturers on Registering Herbal Medicine under the Traditional Herbal Medicine Regulation (THMR)[3]; Guidance on the Use of HMPC Monographs of the Herbal Medicinal Products Committee to Demonstrate Safety and Traditional Use[4]; Organic Herbal Ingredients and Labelling under the Traditional Herbal Medicines Registration (THR) Scheme: Guidance for Applicants/Registration Holders[5]; Guidance on Transitional Arrangements for the Directive on Traditional Herbal Medicinal Products (Directive 2004/24/EC, amending Directive 2001/83/EC)[6]; Registered Traditional Herbal Medicines: Guidance on Consumer Advertising[7]; Guidance on Arrangements for the Transfer of Certain Herbal Products with a Marketing Authorization to Traditional Herbal Registration Status[8]; Public Perceptions of Herbal Medicines: General Public Qualitative and Quantitative Research[9].

The majority of traditional medicines have been sold as food supplements. Therefore, it is important to know how the terms food, food supplements, and medicine are defined regarding their legal, economic, and health aspects. Food can be defined as any substance consumed for nutritional purposes. Food contains carbohydrates, proteins, and fat, to provide the energy for maintenance of life[10]. Food supplements (dietary supplements, nutritional supplements) supplement the diet with components that may be missing or present in insufficient amounts in individual diets, eg, vitamins, minerals, fiber, fatty acids, or amino acids[11]. In the EU, a proof of safety regarding dosage and purity for these supplements is necessary. Food supplements cannot be labeled with drug claims, although general health claims can be made[12]. Medicine (Latin: *ars medica*) is the art of healing and comprises all practices to prevent and heal diseases. If a product's purpose is to heal whatever condition, it is classified as some kind of medicine (pharmacon). Nowadays, aspects of scientific research and technology to diagnose and treat illnesses play a major role in medicine[13].

According to this differentiation, different legislative regulations have been launched by the EU. Food and food supplements are regulated by the EU General Food Law (Regulation EC No. 178/2002)[14], the Novel Foods Regulation (No. 258/97)[15], and the Food Supplements directive (2002/46/EC)[16]. Furthermore, the European Food Safety Authority (EFSA) launched guidelines for botanicals used as food supplements[17]. The Novel Foods Regulation was originally thought for risk assessment of genetically modified food, but applies to any food supplements without significant use prior to the implementation of this regulation in May 1997. Such botanical products are considered as "novel" and require authorization and evaluation for safety by EFSA. It is not beyond the scope of expectation that this regulation might pose even more obstacles to marketing herbal products in Europe than the THMPD. In contrast to the regulations on food and food supplements, medicinal products are regulated by the Human Medicinal Product Directive (HMPD) (2001/83/EC) and the THMPs under the amending directive (2004/24/EC)[1,2].

2 Discussion on pros and cons of the EU directive

The intention of this EU legislation was to establish a regulatory process for high-quality herbal products as medicines rather than food supplements and to allow producers to make restricted medicinal claims on packaging and patient information leaflet. Such herbal medicinal products can be sold without supervision of medical professionals and ensure patients on quality and safety of the products. Considering the numerous reports on toxicity of herbal products with contaminants such as heavy metals, pesticides, organic solvents, microorganisms, etc[18-20], THMPD aimed at providing better protection of patients. For

manufacturers, the EU directive brings more freedom for sales promotion, since certain medicinal claims can be made. If herbal products have been sold as food, cosmetics or general consumer products, manufacturers are allowed to continue selling under these regimens without consideration of the new EU directive under certain conditions.

Safety and quality of herbal medicines is not only relevant to contamination, but also relevant to interaction with other drugs and adverse side effects. These problems have been recently discussed in detail[21,22]. Another problem that is still not covered by THMPD is that unqualified or unregistered practitioners may prescribe unregistered herbs of unsatisfactory quality. This issue still has to be addressed.

Since all herbal preparations with proof of activity and claim for a disease indication need to be registered, the Chinese government stimulated traditional Chinese medicine (TCM) producers to form expert teams and work forces to register TCM products in the EU. However, the implementation process was reluctant. Although the certification and registration process for herbal products is expensive, the registration process for a herbal product may be economically attractive in light of the fact that the TCM export value for TCM products from China to the EU market was 250 million US dollars in the year 2010[23].

The EU directive on traditional remedies from 2004 is already realized in Germany since many years ago. Their Europe-wide ratification in 2011 had no further direct impact in Germany. It is important to notice that individual single prescription of medicinal plants by herbalists and alternative practitioners is further on possible. There is no prohibition of medicinal plants *per se* in Germany or Europe. The EU directive stipulates, however, the registration of complex ready-to-use medications.

Several fears have been raised about the EU directive.

First, the current apprehension is that the distribution of many herbal products derived from non-European traditional medicines such as TCM, Ayurveda or traditional South-American medicines would be massively handicapped, or even prohibited. Critics of the EU directive argue that the standards outside Europe are supposed to be lower leading to a discrimination against non-European herbal medicines, for example, TCM, Ayurveda, Amazonian or African natural medicines and others. This is supposed to be not justified, because these traditional medicines all have a century or millennia-old history speaking for their safety and efficacy.

Second, the requirement of at least 15 years usage in Europe or 30 years outside Europe prevents the use of new herbal combinations that might emerge from scientific research.

Third, the GMP production criteria are difficult to fulfill for many complex poly-herbal mixtures.

Forth, the costs for registration of herbal products may succeed the possibilities of small and medium enterprises and favor "big pharma" in an unbalanced manner.

Fifth, herbal products containing non-herbal ingredients other than vitamins and minerals are disallowed.

Sixth, the costs for registration will make herbal products much more expensive for the user. Some herbal preparations without registration may vanish from the market.

Seventh, the strict EU registration procedures may also have a negative domestic impact on TCM in China.

Eighth, the registration scheme is suited for single herb or limited combinations of herbs which have a long tradition in Europe but not for complex herbal mixtures.

Ninth, novel combinations of herbs are not considered as "traditional" although the plants of such herbal mixtures are part of the traditional medicines.

For these and other reasons, several non-governmental organizations attempted to ameliorate the regulator changes such as the Alliance for Natural Health (http://anh-europe.org/) and the European Benefit Foundation (http://www.benefyt.eu/).

3 Conclusion and perspectives

Frequently, the therapeutic benefits of herbal medicines are supposed to simply reflect placebo effects[24,25]. On the other side, however, herbs can exert considerable toxicities[26]. The only appropriate answer to cope with this challenging opinion is to provide convincing evidence on reliable efficacy and safety of herbal products. This goal can be reached by properly performed clinical trials and evidence-based herbal medicine[27], scientific research on the modes of action of medicinal herbs and natural products[28,29] and high-quality standards of herbal products[30-33].

The EU directives do not generally ban herbal TCM products on the European market as occasionally written in the internet or the public press. To meet high quality and safety measures, the regulations stipulate authorization for commercial herbal products available on the market without consultation of a medical doctor or herbalist. Herbal medicines that are produced on an individual basis for patients after prescription of health care professionals do not require licensing prior to their use. In this case, the legal responsibility for identification and purity is on the side of the pharmacists, the prescription and the individual control of side effects and drug interaction is on the side of the doctor or herbalist.

Quality control will also improve the confidents of patients and customers in herbal products. Quality of herbal preparations does most likely not follow a dichotomic "good/bad" or "yes/no"

scheme, but a Gaussian distribution as most other things in life too. Most herbal medicines are of acceptable quality, but their reputation may suffer from the few "black sheep". An intriguing example was the poisoning of herbal slimming preparations with aristolochic acid more than a decade ago, which led to numerous cases of renal insufficiency and bladder cancer[34-36]. Although the mix-up of *Stephania tetrandra* with the toxic *Aristolochia fangchi* as one component of the herbal mixture was unintended, the reputation of TCM in general suffered from this accident. As a consequence of this poisoning, the term "Chinese herbal nephropathy" was coined, which is not justified at all, since it implies that Chinese herbs in general might be nephrotoxic. Therefore, it is mandatory to provide compelling evidence that not only Chinese herbs, but herbal medicines in general are safe and valuable, if properly applied by well-trained professionals with a deep knowledge on herbal medicine using high-quality products. Both conditions were not given in the *Aristolochia* poisoning.

It can be expected that herbal preparations produced with high-quality standards may even increase sales volume rates in Europe, since they can be used for promotion. The development of product brands, seals of approval, etc, may increase confidence of customers in herbal products, leading to further increasing export rates of TCM products and other herbal preparations to European countries.

4 Competing interests

The authors declare that they have no competing interests.

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欧洲草药禁令对草药疗法的影响

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