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Research Paper

Traditional herbal medicines worldwide, from reappraisal to assessment in Europe ☆

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ABSTRACT

Since 2004 the regulatory framework within the European Union has a specific assessment procedure for herbal medicinal products, with a medicinal use based on traditional practice. The main requirement concerning the traditional use is focussed on the period of time for medical use: at least 30 years, including 15 years in the EU. In addition to requirements for quality and safety, an evaluation of pharmacological effects or efficacy based on long-standing use, is a main objective. "Traditional Use" however encompasses European, and non-European traditional use. Outside the EU, the medicinal use of herbal substances, -preparations, and –combinations is well-known, with a long history, which is well-documented in the different systems of medical practice. This has been addressed by WHO, but it has been acknowledged also by European Commission that herbal products from other systems of medicine, can be subject to the procedure for traditional herbal medicinal products. This paper will focus on the possibilities, restraints, and challenges of regulatory practice in the European Union regarding these category of medicinal products.

1. Introduction

Herbal medicinal products, including traditionally used herbal medicinal products are falling under the scope of the European Directive relating to medicinal products for human use (2001/83/EC). With the amendment in 2004, a specific category of traditional herbal medicinal products was introduced, having regard the particular characteristics of these medicinal products, especially their long tradition (2004/24/EC).

The simplified registration is considered to be acceptable only where the herbal medicinal product may rely on a sufficiently long medicinal use in the European Union. Medicinal use *outside* the European Union should be taken into account only if the medicinal product has been used within the EU for at least 15 years. Where there is limited evidence of use within the EU, it is necessary to assess carefully the validity and relevance of the use in other parts of the World, or within the framework of non-Western systems of traditional medicine. This paper will explore the legal provisions for traditional herbal medicinal products within the EU regulatory framework, when applied to herbal medicinal products based on medicinal use in "non-European" traditions (Table 1).

2. Traditional medicine worldwide

Since 1978 World Health Organization is paying considerable attention to traditional medicine (WHO 1978), with the new WHO traditional medicine strategy 2014–2023 (WHO 2013), described by Zhang Qi in this issue, as most recent development. WHO's strategy makes a stronger emphasis on development of traditional medicine, instead of a focus on traditional medicinal products, as in the EU regulatory framework. *"Traditional medicine"* is defined by WHO as: *"Traditional medicine has a long history. It is the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness* (WHO http://www.who.int/medicines/areas/traditional/definitions/en/). Although sometimes traditional knowledge, skills, and practices are far away from the principles of Western scientific medicine, the place of traditional medicine has not been ignored when the European framework for traditional

Abbreviations used: ANVISA, Agência nacional de vigilância sanitária, Brazil; EMA, European medicines agency; EU, European union; HMPC, Committee on herbal medicinal products; HAS, Health science authority, Singapore; PDMA, Pharmaceutical and medical devices agency, Japan; TCM, Traditional chinese medicine; WHO, World health organization

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Table 1
Examples of traditional medicine worldwide.

Ayurvedic medicine	Traditional Chinese Medicine (TCM)	Use of medicinal plants in:
Siddha medicine	Tibetan, Mongolian, Uighur medicine	Vietnam and Laos
Unani medicine	Traditional African Medicine	South Africa
Arabic medicine	Traditional Korean Medicine	South Pacific
Kampo medicine	Traditional Thai Medicine	Indonesia
gSo-ba Rig-pa – Bhutanese medicine	Traditional medicine of native Indians, in North and South America	Guiana's: Guyana, Surinam, French Guiana
Australian bush medicine	Rongoā – traditional Maori medicine	Papua New Guinea

Table 2
Ways of interpretation of article 16a (1)e Directive 2001/83/EU.

The data on the tradition of the medicinal use of the product are sufficient;	*The justification of the tradition of the medicinal use of the active substance is sufficient;*
In particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy are scientifically justified and are plausible. There is a long-standing use and tradition.	*In particular the traditional use and the long experience demonstrate that the product is not harmful and the pharmacological effects or efficacy are made plausible for the specified active constituents and are in accordance with the principles of the specific medical tradition.*

herbal medicinal products based upon long-standing use, was established in 2004. In this paper the focus will remain on "medicinal products", subject to the regulatory system in the European Union. However, numerous products from non-European traditions are on the markets of the EU Member States, without regulation on quality, safety, and the medicinal use.

3. European legislation and intentions

In "Communication from the Commission to the Council and the European Parliament concerning….specific provisions applicable to traditional herbal medicinal products", published in 2008 (COM 584), extensive clarification was given on the backgrounds for traditional medicines, used in other parts of the world than the European Union, as well as the considerations of the legislator. As main examples, Ayurveda and Traditional Chinese Medicine are mentioned, for both it is obvious that the European Commission is aware of the long tradition outside Europe ("have existed for centuries in other parts of the world" – COM 584), the concepts of healing of both, and to what extend the simplified procedure for traditional herbal medicinal products could be followed to get a registration in the EU.

When speaking of a possible extension of the scope for medicinal products based on long-standing use and experience this is, for example related to "certain medicinal products from specific….*non*-European medicine systems (such as..Ayurvedic, Chinese, Kampo, Korean, Mongolian, Thai, Tibetan, Unani, or Vietnamese medicine" – COM 584), but it is not clarified which medicinal products from non-European medicine systems already are eligible for the simplified registration procedure with a view to placing them on the market as traditional medicinal products. And those, which are not.

The simplified registration for an herbal medicinal product is acceptable only where the product may rely on at least 30 years of medicinal use. Medicinal use outside the European Union can be taken into account only if the medicinal product has been used in the European Union for at least 15 years.

4. Assessment of traditional herbal medicinal products

Assessment following the specific provisions applicable to traditional herbal medicinal products (art. 16a (1), 2001/83/EC) is possible for a herbal medicinal product with indications used without the supervision of a medical practioner for diagnostic purposes or for prescription or monitoring of treatment; in accordance with a specified strength and posology; by oral, external and/or inhalation preparation; the medicinal product has been in use throughout period of at least 30 years preceding the date of application, including at least 15 years with the European Union. Especially in cases of doubt regarding the evaluation of the period of time, specific referral procedures have been established (NtA Vol.2A), in which the Herbal Medicinal Products Committee can draw up an opinion, if requested by a Member State.

The core of the scientific assessment is expected to give an opinion whether the data of the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful under the specified conditions of use and the pharmacological effects *or* efficacy of the medicinal product *are* plausible on the basis of long-standing use and *tradition*. (art. 16a (1)e, 2001/83/EC). Taking into account the limitation of the scope of this procedure, there is no doubt that this basis for assessment is applicable for medicinal products used in both a European tradition, and in a non-European tradition. For all traditional herbal medicinal products, the long-standing use and the tradition has to be assessed. Since the establishment of the specific provisions, very limited experience is gained in Member states for medicinal products from non-European traditions (Table 2).

For applications for traditional herbal medicinal products, the competent authority lies at the Member States of the EU. During the last years only a very few applications have been assessed for medicinal products with a tradition outside the European Union. Only Diao Xin Xue Kang capsules were successfully registered in the Netherlands, but according to the public announcement and the published Public Assessment Report (CBG-PAR 2012- http://db.cbg-meb.nl/Pars/h102142.pdf), the assessment by the Dutch MEB does not give an opinion about the principles of TCM. Until now, no Referral procedures are initiated at the HMPC, for herbal medicinal products from non-European traditions as well. More national applications and an appropriate use of the Referral procedures for traditional herbal medicinal products could increase the regulatory experience on relevant issues.

5. Community herbal monographs and non-European traditions

The Committee on Herbal Medicinal Products shall establish Community herbal monographs for herbal medicinal products