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The Globalization of Traditional Medicines: Perspectives Related to the European Union Regulatory Environment

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ABSTRACT

In the Member States of the European Union (EU), a harmonized legislation on medicinal products has been enforced, which specifically defines herbal medicinal products and traditional herbal medicinal products. The scope was to create a regulatory environment that takes into account the particular characteristics of herbal medicinal products. The harmonization of standards is intended to harmonize assessment and facilitate access to the market in different Member States. The standards defined by the EU herbal monographs of the Committee on Herbal Medicinal Products (HMPC) and the quality requirements laid down in the *European Pharmacopoeia* represent an excellent model of multinational harmonization of the regulatory environment for herbal and traditional medicines. It has also been demonstrated that this framework is at least partially applicable for herbal and traditional medicines from traditional Chinese medicine (TCM) to gain access to the EU market. Moreover, the HMPC provides specific guidance documents and pilot projects on monographs on the safety and efficacy of Chinese herbal drugs. In the *European Pharmacopoeia*, the number of quality monographs of herbal drugs with an origin in TCM is continuously growing. These developments indicate that globalization of traditional medicines is an ongoing process. Communication and cooperation between regulators, the scientific community, and interested stakeholders will set the stage for the convergence of diverse regulatory environments. This will contribute to worldwide availability of traditional medicines based on appropriate standards.

1. Introduction

The intention of this article is to provide information on the regulation of herbal and traditional medicines in the European Union (EU) regulatory framework. In particular, it gives a perspective on the challenges of globalization and on the options of and interactions between traditional medicines from Asia, such as traditional Chinese medicine (TCM).

1.1. Herbal and traditional medicines

Traditional medicines, and especially the usage of medicinal plants, have been a part of human history all over the world [1], with knowledge being transferred from generation to generation. In some parts of the world, such as Asia and Europe, written documentation can be traced back to ancient times [2]. For example, the so-called *Shennong Bencao Jing* (literally the *Shennong's Classic of Materia Medica*), which originated in China, is a famous collection of the traditional use of 365 drugs, and in ancient Greece, Dioscurides reported on therapeutic use of about 600 medicinal plants [2–4]. A worldwide trade of selected medicinal plants began as traffic increased along major trade routes between Europe, Asia, and other continents.

At present, herbal and traditional medicines are contributing to healthcare in many countries around the world [2]. There is a general, global, and growing interest in the integration of herbal and traditional medicines; such integration often includes herbal medicines as one therapeutic option in addition to, for example, nutrition, physical treatment, or therapeutic movement.

1.2. Regulation, definitions, and classification

The terms *herbal medicines* and *traditional medicines* are common to both lay people and scientists. However, there is a large diversity of regulatory frameworks around the world. The World Health Organization (WHO) Traditional Medicine Strategy 2014–2023 provides the following set of definitions [5]:

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Traditional and complementary medicine

Traditional and complementary medicine include herbs, herbal materials, herbal preparations, and finished herbal products that contain parts of plants, other plant materials, or combinations thereof as active ingredients.

Traditional medicine

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.

Complementary medicine

The terms "complementary medicine" or "alternative medicine" refer to a broad set of healthcare practices that are not part of that country's own tradition or conventional medicine and are not fully integrated into the dominant healthcare system. They are used interchangeably with traditional medicine in some countries.

Accordingly, there is a need to differentiate between "traditional medicine," which is a term referring to a complex therapeutic setting, and "traditional medicines," which can be interpreted as the medicinal products that are used within a specific traditional medicine.

With respect to existing regulatory frameworks, there is no globally accepted set of definitions. Instead, due to the regional usage of traditional and herbal medicines, there is a broad diversity of regulatory systems for traditional and herbal medicines in different countries. As all concepts consider regional developments, the concepts cannot be defined as "right" or "wrong." This diversity is also visible in terminology and classification. For example, regulation in Canada uses the term "natural health products" for a rather broad group of products that include vitamins and minerals. In the United States, the term "botanicals" is applied, but very few medicinal products are authorized as botanical drugs; the major part of the market is dominated by so-called "dietary supplements." In Asia, TCM, Ayurvedic medicine, and Kampo medicine provide particular classifications and definitions. Definitions of herbal medicinal products and traditional herbal medicinal products in the EU are presented in detail in Section 3.1.

1.3. Challenges of globalization

A first historic trend toward the globalization of herbal medicines and traditional medicines was linked to the trade along important terrestrial or sea routes during the Middle Ages. Nowadays, global trade of products is common. There is a worldwide trend to use herbal and traditional medicines, and to apply therapeutic systems based on a traditional origin, such as TCM. Companies face great challenges when trying to gain access to different markets for herbal medicines. They must follow different legislations and accept different requirements and diverse standards. As a result, for the same products, pharmaceutical companies have to develop different dossiers to present them to different national authorities. International communication within the scientific community and regulators are necessary to develop appropriate regulatory environments for herbal and traditional medicines.

2. Understanding the multinational regulatory network in the EU

2.1. Key institutions of the network

In the EU, there is a harmonized regulatory framework for medicinal products in all Member States. The basic rules are laid down in Directive 2001/83/EC [6], which can be seen as a European law on medicinal products, and which was implemented into the national frameworks of each Member State. In addition to the overall scope of sharing responsibility in an important field of public health, this harmonized legislation was created to facilitate access to the market and to establish defined procedures for work-sharing between national competent authorities.

The competence to establish European legislation lies with the European Parliament and the European Commission. Although "regulations" are laws that are immediately binding in the Member States, "directives" must be implemented by national legislation. Important key institutions within this network are the European Directorate for the Quality of Medicines & HealthCare (EDQM, Strasbourg, France), the European Medicines Agency (EMA, which is currently in London, UK, but will be in Amsterdam, the Netherlands, as of March 2019), and the competent national authorities of the Member States (e.g., the Federal Institute for Drugs and Medical Devices in Germany (BfArM)). This network is a complex one (Fig. 1), and a company must understand the necessary responsibilities if it wants to apply for access to the market.

2.2. EDQM

The EDQM is an institution that supports the implementation and monitoring of the application of quality standards on medicinal products [7]. Harmonized standards are published in the *European Pharmacopoeia* after adoption by the European Pharmacopoeia Commission [8]. Members of the European Pharmacopoeia Commission include other countries as well as the EU Member States, and a further group of countries contributes as observers. The quality requirements defined in the *European Pharmacopoeia* are binding standards within the EU. The EDQM also provides reference standards for assays and tests. For pharmaceutical substances, the EDQM grants certificates of suitability, which confirm compliance with the standards of the *European Pharmacopoeia* and which can be part of the dossiers within an authorization procedure. The EDQM coordinates a network of Official Medicines Control Laboratories in order to collaborate and pool expertise, and to effectively use limited resources with the aim of achieving effective public quality control of medicines.

With respect to herbal medicinal products in the EU, the *European Pharmacopoeia* provides general monographs and specific monographs on herbal drugs or herbal drug preparations. These monographs address all quality issues related to herbal drugs and herbal drug preparations, such as methods, tests, identification, assays, heavy metals, aflatoxins, pesticides, and microbial contamination. Specific expert groups (i.e., 13 A, 13 B, and TCM) have been

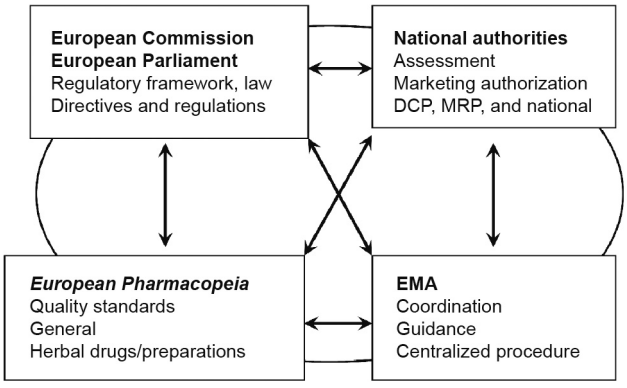

Fig. 1. Key EU institutions contributing to the legal framework on medicinal products. DCP: decentralized procedure; MRP: mutual recognition procedure.

established at the EDQM to elaborate monographs on herbal drugs and/or herbal preparations.

2.3. EMA

The EMA was established more than 20 years ago. Its major objective is to coordinate the network of competent national authorities on medicinal products within the EU. Within this framework, there are different procedural options. Some procedures are run at the EMA, while other procedures are organized on a national level and provide the option of procedures, which are jointly organized by a subset of Member States. Different topics of relevance for medicinal products are currently covered by seven scientific expert committees (Table 1) [9].

Depending on their particular tasks, the committees have substructures, including working parties and drafting groups. Overall, the administrative and scientific staff members of the EMA, along with national experts and institutions, are contributing to a high level of assessment and harmonized decision-making within the EU. Of course, the principle of work-sharing and the responsibility for public health are not limited to evaluation before market access. Early steps such as scientific advice during drug development, the approval and control of clinical trials, post-marketing maintenance and monitoring of risks, and enforcement of actions are other important activities that are shared across the EU. The emphasis on the establishment of the Committee on Herbal Medicinal Products (HMPC) demonstrates that the European Commission is aware of the substantial interest of the EU population in having the option of the availability of such products.

2.4. Options for medicinal products to access the market within the EU

The basic approach in the EU is to assess the quality, efficacy, and safety of herbal medicinal products or traditional herbal medicinal products before they have access to the market. The pharmaceutical company must choose an appropriate procedure to file an application for marketing authorization or registration. The following procedures are legally established [6,10]:

- **Centralized procedure (CP)**. This procedure for marketing authorization is directed to the EMA and is linked to an assessment coordinated by EMA. If the marketing authorization is granted, a medicinal product can be marketed in all Member States of the EU. This procedure is utilized when there is a defined set of indications (e.g., oncological or neurological indications) or medicinal products of special importance for public health.
- **Decentralized procedure (DCP)**. This procedure for marketing authorization or registration is directed to a subset of Member States. A Reference Member State takes the lead for the assessment and the other Member States involved (i.e., the Concerned Member States) mainly check the assessment by the Reference Member State. At the end of a successful procedure, a marketing authorization or registration is granted in the participating Member States.
- **Mutual Recognition Procedure (MRP)**. If a medicinal product is already authorized or registered in one Member State, a procedure may be initiated that is built upon the existing assessment. At the end of a successful procedure, a marketing authorization or registration is granted in the participating Member States.
- **National procedure**. An application can be directed to a single national competent authority; at the end of a successful procedure, a marketing authorization or registration for only one Member State is granted.

An application must be submitted electronically and in a distinct format, as a Common Technical Document. The content depends on the type of procedure, as described above, and on the type of application: ① Marketing authorization: full application—for new medicinal products, bibliographic application—for known medicinal products with well-established use, and hybrid forms may be used; ② Registration: Bibliographic application with additional data on safety if necessary—only for traditional herbal medicinal products.

Table 1
Scientific committees at the EMA.

Acronym	Name
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
PDCO	Paediatric Committee
HMPC	Committee on Herbal Medicinal Products
CAT	Committee for Advanced Therapies
CVMP	Committee for Medicinal Products for Veterinary Use
PRAC	Pharmacovigilance Risk Assessment Committee

3. Establishment of harmonized standards for herbal and traditional medicines in the EU

3.1. Basic legal documents and definitions

In the EU, basic definitions are laid down in Directive 2001/83/EC [6]. The European regulatory framework provides definitions for herbal medicinal products, traditional herbal medicinal products, herbal substances, and herbal preparations:

Herbal medicinal products
Any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Traditional herbal medicinal products
An herbal medicinal product that fulfils the conditions laid down in Article 16a(1) of Directive 2001/83/EC [6]. Vitamins and minerals may be added if their action is ancillary to the herbal constituent(s). [As this is the original basic definition, no further explanation is given here; however, the approach and criteria are described in more detail in Section 3.3 in the context of the concept of traditional use.]

Herbal substances
[synonym "herbal drug" according to the *European Pharmacopoeia* [8]]
All mainly whole, fragmented, or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety, and author).

Herbal preparations
[synonym "herbal drug preparation" according to the *European Pharmacopoeia* [8]]
Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration, or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices, and processed exudates.

3.2. HMPC: Composition and workflow on monographs

The HMPC is the scientific committee of the EMA, and is responsible for tasks related to herbal medicinal products. At present,

there are 28 delegates to the HMPC, one delegate nominated by each Member State of the EU, and five so-called "coopted members," who provide additional expertise, such as in the field of pediatrics, toxicology, pharmacology, clinical pharmacology, and general medicine. The EMA coordinates the work of the committee and provides a secretariat. If necessary, coordination is initiated with other committees established within the EMA.

The main task of the HMPC is the establishment of EU herbal monographs, which address the efficacy and safety of herbal substances or the herbal preparations derived thereof. A monograph is drafted by a rapporteur who takes into account all data that are publicly available or provided by the national competent authorities. During the development of a monograph, the scientific content is discussed at the Working Party on European Union Monographs and European Union List and at the HMPC. A peer review is installed to ensure the quality and consistency of the documents. Stakeholders and the scientific community have the option to contribute to the development: ① in the initial stages, by providing data when a "call for scientific data" is published; or ② by commenting on drafts, which are made available for a three-month period of public consultation. After final adoption, the EU herbal monograph, a list of references, the assessment report, and an overview of comments received during the consultation period are published by the EMA [9].

3.3. Monographs and guidance established by the HMPC

The EU herbal monographs of the HMPC represent a harmonized position, and should facilitate the marketing authorization of herbal medicinal products and the registration of traditional herbal medicinal products in the Member States of the EU. The structure of the monographs mirrors the content of a summary of product characteristics. This includes all relevant information regarding safety and efficacy. As a result, the monographs provide the national competent authorities with a recommendation as a basis for a product-specific assessment.

The following list displays the main sections of an EU herbal monograph:

- *Qualitative and quantitative composition*
- *Pharmaceutical form*
- *Clinical particulars*
  - *Therapeutic indications*
  - *Posology and method of administration*
  - *Contraindications*
  - *Special warnings and precautions for use*
  - *Interactions*
  - *Pregnancy and lactation, fertility*
  - *Effects on the ability to drive and use machines*
  - *Undesirable effects*
  - *Overdose*
- *Pharmacological properties*
  - *Pharmacodynamic properties*
  - *Pharmacodynamic properties*
  - *Pharmacokinetic properties*
  - *Preclinical safety data*
- *Pharmaceutical particulars*

Depending on the existing data, a monograph may assign an herbal substance or an herbal preparation to two different categories. The two categories follow either the concept of well-established use or the concept of traditional use.

3.3.1. The concept of well-established use

The concept of well-established use was implemented in European legislation not only for herbal medicinal products, but also for other medicinal products that were already on the market when the legislation was developed. The basic approach is to demonstrate with sound bibliographic data that the medicinal product has a well-established medicinal use with recognized efficacy and an acceptable level of safety. For this type of application, it is not necessary to provide one's own results from toxicological and pharmacological tests or clinical trials. Instead, published scientific literature is discussed in expert reports on nonclinical and clinical data. The time of accepted medicinal use in the EU must be at least ten years. The HMPC has established a particular guideline on the assessment of clinical safety and efficacy with respect to this concept [9]. According to the guideline, at least one controlled clinical study (i.e., clinical trial, post-marketing study, or epidemiological study) of good quality is required in order to substantiate efficacy for a well-established use herbal monograph.

3.3.2. The concept of traditional use

A particular legislation, Directive 2004/24/EC [11], was created as an amendment to the overall Directive 2001/83/EC [6] in order to provide a particular framework for traditional medicines. The European Commission was concerned that the requirements established for all medicinal products could not be fulfilled by traditional medicines because of their particular characteristics. The approach was to offer the option of a so-called simplified registration for traditional medicines that have a long tradition of medical usage, thus replacing particular requirements for safety and efficacy. The time to establish a tradition was set at 30 years, during at least 15 of which a product should have been in medicinal use in the EU. The second part of the 15 years of medicinal use could also be in the EU, or could be demonstrated for any other part of the world. Following the precautionary principle, a set of inclusion criteria was established to guarantee safety and an appropriate application of traditional herbal medicinal products:

- Indication(s) appropriate to traditional herbal medicinal products;
- Use without the supervision of a medical practitioner for diagnosis, prescription, or monitoring of treatment;
- Specified strength/posology;
- Only oral use, external use, and inhalation;
- Sufficient data on traditional use of the product (to demonstrate safety); and
- Pharmacological effects/efficacy that are plausible on the basis of longstanding use and experience.

Additional data on safety may be requested by national authorities. There is no difference in requirements on quality. The quality of traditional herbal medicinal products must meet the same criteria as any other herbal medicinal products. A specific labeling for traditional herbal medicinal products is defined in the legislation. The package leaflet must include a statement that the product is a traditional herbal medicinal product for use with specified indications exclusively based upon longstanding use, and that the user should consult a doctor or qualified healthcare practitioner if the symptoms persist during the use of the product or if adverse effects that are not mentioned in the package leaflet occur.

Depending on the concept of an application for an herbal medicinal product, there are different requirements. Fig. 2 presents an overview of the requirements assigned to applications for new herbal medicinal products, for herbal medicinal products with well-established use, and for the registration of traditional herbal medicinal products.

The HMPC also halts projects, in cases where a monograph could not be finalized. If there is a general lack of sufficient data, projects are routinely put on hold. If there are legal reasons safety concerns regarding the development of an herbal monograph, the HMPC issues a public statement describing these reasons and offers the option to proceed when new data is available. As of

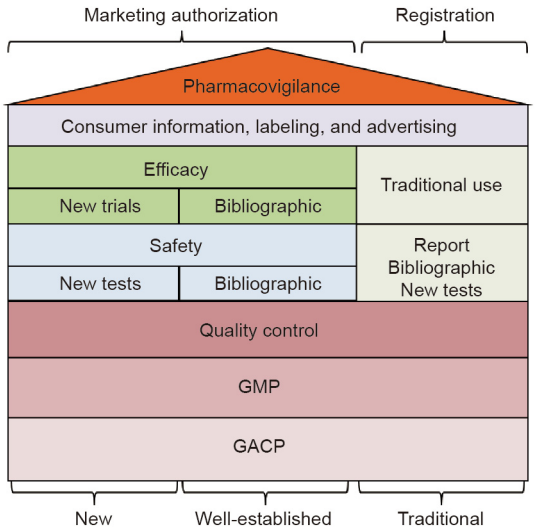

Fig. 2. An overview of the requirements for applications for marketing authorization or registration of herbal medicinal products in the EU. GMP: good manufacturing practice; GACP: good agricultural and collection practice.

July 2018, the HMPC has released more than 155 monographs, 13 List Entries and 21 Public Statements on herbal substances. The majority of the monographs resulted in an assignment of traditional use, 13 monographs concluded well-established and traditional use for different herbal preparations of an herbal substance, and 13 monographs concluded for well-established use only. An overview of the results of selected examples is given in Tables 2 and 3 [9].

The work of the HMPC on monographs and List Entries is complemented by a large set of guidance documents, which support the interpretation of the legislation and which define requirements on particular issues in detail. These documents may cover all aspects of quality, safety, and efficacy. The documents reflect the current status of knowledge and methodology, and are published as guidelines, question-and-answer documents, or reflection papers. A selection of these documents that represents their diversity is displayed in Table 4 [9]. All guidance documents elaborated by the HMPC are published on the EMA website.

4. Current situation and regulatory activities concerning TCM in the EU regulatory framework

The citizens of the EU already have different options to access TCM, although these options may differ in detail at the national level. In Germany, there is a network of pharmacies offering access to about 250 Chinese herbal medicines. Healthcare professionals with an education in TCMs can provide prescriptions for individual mixtures. Certain specialized hospitals offer treatment based on TCM. Some general hospitals with special units on natural medicine integrate different elements of TCM, including acupuncture, physical therapies such as Qigong, a focus on diet and nutrition, and the use of TCMs. Some of these TCMs may be legally imported, while others are provided in gray zones of the Internet. In some cases, there are serious problems with quality issues. In summary, TCM is already present in the EU to a certain extent. Logically, it is important to analyze which options are available for access to the market in the field of medicinal products.

The original scope of European legislation on traditional herbal medicinal products was to offer an option for products with substantial medical use in Europe. However, the consequences of globalization, such as the existence of different therapeutic systems and products from TCM or other therapeutic systems, have motivated the HMPC to include issues related to non-European traditional medicines into the work program. A question-and-answer document was released in 2014 that explained the European regulatory framework and the options and limitations for traditional products originating from non-European regions [9]. That document was a compilation of essential parts of European legislation, and provided a first orientation. The HMPC also started pilot projects on Paeoniae radix alba, Paeoniae radix rubra, Centellae asiaticae herba, Angelicae sinensis radix, and Picrorhizae kurroae rhizoma et radix in order to check the option of a development of an herbal monograph in the EU regulatory framework. These projects have not led to a monograph thus far, for reasons that are explained in public statements. It is still possible that the drafting of the monograph will continue when adequate data are available. In some cases, the tradition with respect to EU legislation is not appropriately proven; in some cases, the herbal preparations are not sufficiently described; and in some cases, the indications do not fit the requirements. The experts in the EU are doubtless aware of the existing set of scientific data, but the pilot projects revealed the challenges of bringing different therapeutic traditions into different regulatory environments.

Another, and more successful, project was the integration of monographs on herbal drugs from TCM into the *European Pharmacopoeia*. In order to contribute to convergence of quality requirements and to define legally binding standards for herbal drugs from TCM marketed in the EU (in all members of the European Pharmacopoeia Convention, respectively), the *European Pharmacopoeia* [8] has established a particular expert group to elaborate Pharmacopoeia monographs for herbal substances originating in TCM. As of the spring of 2018, this expert group has prepared 73 monographs for TCM herbal substances for adoption by the European Pharmacopoeia Commission. This set of harmonized monographs on quality is a milestone in improving the availability of herbal drugs from TCM. Further herbal drugs from TCM will be included. Table 5 [8] provides an overview on the monographs that have been established to date. The corresponding Section 5.22 in the *European Pharmacopoeia* only addresses recently established monographs on herbal drugs from TCM. Herbal drugs such as ginseng root, which have a longstanding history in Europe, are not a part of this project.

The European regulatory framework does not only offer options for access to Chinese herbal medicines; it also sets limitations. The particular framework for traditional herbal medicinal products is not suitable for active substances of animal origin. The route of administration is restricted to oral administration, external use, and inhalation. Therefore, injections, which are quite common in TCM, cannot be granted a registration as traditional herbal medicinal products. Finally, registration is limited to minor diseases and is usually not designed for chronic application. Nevertheless, in some cases, registration as traditional herbal medicinal products has already been granted for products from TCM, such as capsules containing an aqueous dry extract of the dried rhizomes of *Dioscorea nipponica*, tablets containing an aqueous dry extract of dried aerial parts of *Siegesbeckia orientalis*, and capsules containing an ethanolic dry extract from the roots of *Salvia miltiorrhiza*. As the first three examples of successful registration of traditional herbal medicinal products in the Netherlands and in the United Kingdom, these registrations clearly demonstrate that it is possible to have access to the market in the EU on the platform provided by EU legislation. Further registrations have been granted, and applications are under assessment.

Table 2
Selected herbal substances evaluated by the HMPC resulting in a monograph or a list entry [9].

Categories	Herbal substance (Latin name)	Botanical name of plant	Common name
T	Millefolii herba	*Achillea millefolium* L.	Yarrow
T, W	Hippocastani semen	*Aesculus hippocastanum* L.	Horse-chestnut seed
W	Aloes folii succus siccatus	*Aloe barbadensis* Mill. and *Aloe* (various species, mainly *Aloe ferox* Mill. and its hybrids)	Aloes
T	Arnicae flos	*Arnica montana* L.	Arnica flower
T	Absinthii herba	*Artemisia absinthium* L.	Wormwood
T	Betulae folium	*Betula pendula* Roth/*Betula pubescens* Ehrh.	Birch leaf
T, LE	Calendulae flos	*Calendula officinalis* L.	Calendula flower
T	Camelliae sinensis non fermentatum folium	*Camellia sinensis* L.O. Kuntze	Green tea leaf
W	Capsici fructus	*Capsicum annuum* L. var. *minimum* (Miller) Heiser	Capsicum
W	Cimicifugae rhizoma	*Cimicifuga racemosa* (L.) Nutt.	Black cohosh
T	Cinnamomi cortex	*Cinnamomum verum* J.S. Presl (*Cinnamomum zeylanicum* Nees)	Cinnamon
T	Colae semen	*Cola nitida* (Vent.) Schott & Endl. and its varieties and *Cola acuminata* (P. Beauv.) Schott & Endl.	Cola
T,W	Combination: Valerianae radix and Lupuli flos	Combination: *Valeriana officinalis* L. and *Humulus lupulus* L.	Valerian root and hop strobile
T	Myrrha, gummi-resina	*Commiphora myrrha* Engl.	Myrrh
T	Cucurbitae semen	*Cucurbita pepo* L.	Pumpkin seed
T	Curcumae longae rhizoma	*Curcuma longa* L.	Turmeric
T	Cynarae folium	*Cynara scolymus* L.	Artichoke leaf
T, W, LE	Echinaceae purpureae herba	*Echinacea purpurea* (L.) Moench	Purple coneflower herb
T, LE	Eleutherococci radix	*Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim.	Eleutherococcus root
T, LE	Foeniculi amari fructus	*Foeniculum vulgare* Mill. subsp. *vulgare* var. *vulgare*	Bitter fennel
T	Fucus vesiculosus, thallus	*Fucus vesiculosus* L.	Bladderwrack
T	Gentianae radix	*Gentiana lutea* L.	Gentian root
T, W	Ginkgo folium	*Ginkgo biloba* L.	Ginkgo leaf
T	Soiae oleum raffinatum	*Glycine max* (L.) Merr.	Soya-bean oil, refined
T	Liquiritiae radix	*Glycyrrhiza glabra* L. and/or *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch.	Liquorice root
W	Hederae helicis folium	*Hedera helix* L.	Ivy leaf
T, W	Hyperici herba	*Hypericum perforatum* L.	St. John's Wort
T	Leonuri cardiacae herba	*Leonurus cardiaca* L.	Motherwort
T	Levistici radix	*Levisticum officinale* Koch.	Lovage root
T, W	Lini semen	*Linum usitatissimum* L.	Linseed
T	Matricariae flos	*Matricaria recutita* L.	Matricaria flower
T, LE	Melaleucae aetheroleum	*Melaleuca alternifolia* (Maiden & Betch) Cheel, *M. linariifolia* Smith, *M. dissitiflora* F. Mueller, and/or other species of *Melaleuca*	Tea-tree oil
T,	Menthae piperitae folium	*Mentha* × *piperita* L.	Peppermint leaf
T, W, LE	Menthae piperitae aetheroleum	*Mentha* × *piperita* L.	Peppermint oil
T	Ginseng radix	*Panax ginseng* C.A. Meyer.	Ginseng root
T	Passiflorae herba	*Passiflora incarnata* L.	Passion flower
T	Pelargonii radix	*Pelargonium sidoides* DC. and *Pelargonium reniforme* Curt.	Pelargonium root
W	Plantaginis ovatae semen	*Plantago ovata* Forssk.	Ispaghula seed
T	Primulae flos	*Primula veris* L. and *Primula elatior* (L.) Hill	Primula flower
T	Pruni africanae cortex	*Prunus africana* (Hook f.) Kalkm.	Pygeum africanum bark
T	Quercus cortex	*Quercus robur* L., *Quercus petraea* (Matt.) Liebl., and *Quercus pubescens* Willd.	Oak bark
W	Rhei radix	*Rheum palmatum* L. and *Rheum officinale* Baillon	Rhubarb
T	Rhodiolae roseae rhizoma et radix	*Rhodiola rosea* L.	Arctic root
W	Ricini oleum	*Ricinus communis* L.	Castor oil
T, W	Salicis cortex	*Salix* (various species including *S. purpurea* L., *S. daphnoides* Vill., and *S. fragilis* L.)	Willow bark
T	Salviae officinalis folium	*Salvia officinalis* L.	Sage leaf
T, W	Sabalis serrulatae fructus	*Serenoa repens* (W. Bartram) Small	Saw palmetto fruit
T, LE	Sideritis herba	*Sideritis scardica* Griseb., *Sideritis clandestina* (Bory & Chaub.) Hayek, *Sideritis raeseri* Boiss. & Heldr, and *Sideritis syriaca* L.	Ironwort
T	Caryophylii floris aetheroleum	*Syzygium aromaticum* (L.) Merill et L.M. Perry	Clove oil
T, LE	Thymi aetheroleum	*Thymus vulgaris* L. and *Thymus zygis* Loefl. ex L.	Thyme oil
T, W, LE	Valerianae radix	*Valeriana officinalis* L.	Valerian root
T, W	Agni casti fructus	*Vitex agnus-castus* L.	Agnus castus fruit
T, W, LE	Vitis viniferae folium	*Vitis vinifera* L.	Grapevine leaf
T, W	Zingiberis rhizoma	*Zingiber officinale* Roscoe	Ginger

T: traditional use monograph; W: well-established use monograph; LE: list entry.

5. Key steps for projects for traditional medicines to apply for registration as traditional herbal medicinal products or for marketing authorization as herbal medicinal products in the EU

This section focuses on certain important key steps that are relevant for those who are considering a project linked to the access of herbal or traditional medicines to the European market. An essential precondition is a basic understanding of the EU network, legislation, and particular guidance. First, the classification of the product must be decided. The information provided in this article focuses on basic classification as medicinal products. EU legislation on food, cosmetics, or medical devices is not covered. Within the field of medicinal products, the next step is the appropriate type of application linked to the question: Is there an option for

Table 3
Herbal substances evaluated by the HMPC resulting in a Public Statement [9].

Herbal substance (Latin name)	Botanical name of plant	Common name
Adhatodae vasicae folium	*Adhatoda vasica* Nees	Malabar-nut leaf
Allii cepae bulbus	*Allium cepa* L.	Onion
Andrographidis paniculatae folium	*Andrographis paniculata* Nees	Kalmegh
Angelicae sinensis radix	*Angelica sinensis* (Oliv.) Diels	Angelica sinensis root
Centellae asiaticae herba	*Centella asiatica* L. Urban	Centella
Chelidonii herba	*Chelidonium majus* L.	Greater celandine
Citri bergamiae aetheroleum	*Citrus bergamia* Risso & Poiteau.	Bergamot oil
Euphrasiae herba	*Euphrasia officinalis* L. and *Euphrasia rostkoviana* Hayne	Eyebright
Balsamum peruvianum	*Myroxylon balsamum* (L.) Harms var. *perierae* (Royle) Harms	Peru balsam
Paeoniae radix rubra	*Paeonia lactiflora* Pall. or *Paeonia veitchii* Lynch	Red peony root
Paeoniae radix alba	*Paeonia lactiflora* Pallas	White peony root
Picrorhizae kurroae rhizoma et radix	*Picrorhiza kurroa* Royle ex. Benth.	Katula
Piperis methystici rhizoma	*Piper methysticum* G. Forst.	Kava kava
Salviae fruticosae folium	*Salvia fruticosa* Mill.	Three-lobed sage leaf
Salviae officinalis aetheroleum	*Salvia officinalis* L.	Sage oil
Sambuci fructus	*Sambucus nigra* L.	Elderberry
Caryophylii flos	*Syzygium aromaticum* (L.) Merill et L.M. Perry	Clove
Tiliae tomentosae flos	*Tilia tomentosa* Moench	Silver lime flower
Uncariae tomentosae cortex	*Uncaria tomentosa* (Willd. ex Schult.) DC.	Cat's Claw
Visci albi herba	*Viscum album* L.	Mistletoe
Withaniae somniferae radix	*Withania somnifera* (L.) Dunal	Winter-cherry root

Table 4
Selected guidance documents published by EMA/HMPC [9].

Document type	Guideline documents
On quality	• Declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products, EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1 • Good agricultural and collection practice for starting materials of herbal origin, EMEA/HMPC/246816/2005 • Quality of combination herbal medicinal products/traditional herbal medicinal products, EMEA/HMPC/CHMP/CVMP/214869/2006 • Quality of herbal medicinal products/traditional herbal medicinal products, EMA/HMPC/201116/2005 Rev. 2 • Specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations, and herbal medicinal products/traditional herbal medicinal products, EMA/HMPC/162241/2005 Rev. 2 • Questions and answers on quality of herbal medicinal products/traditional herbal medicinal products, EMA/HMPC/41500/2010 Rev.5 • Level of purification of extracts to be considered as herbal preparations, EMA/HMPC/186645/2008 • Markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products, EMEA/HMPC/253629/2007
On nonclinical and clinical issues	• Assessment of genotoxicity of herbal substances/preparations, EMEA/HMPC/107079/2007 • Selection of test materials for genotoxicity testing for traditional herbal medicinal products/herbal medicinal products, EMEA/HMPC/67644/2009 • Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products, EMA/HMPC/104613/2005–Rev.1 • Clinical assessment of fixed combinations of herbal substances/herbal preparations, EMEA/HMPC/166326/2005
On safety issues	• Contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids, EMA/HMPC/328782/2016 • Environmental risk assessment of herbal medicinal products, EMA/HMPC/121934/2010 • Use of herbal medicinal products containing pulegone and menthofuran, EMA/HMPC/138386/2005 Rev. 1 • Use of herbal medicinal products containing thujone, EMA/HMPC/732886/2010 Rev.1

registration as a traditional herbal medicinal product, or will the application be based on a new active substance?

For any medicinal product, including herbal medicinal products, there is an option for a full application. This approach requires a complete set of data covering quality, as well as nonclinical and clinical development for a new active substance. Resources should be available, as for any other drug development. For distinct indications, such as diabetes, cancer, neurodegenerative disorders, or antivirals, there is an obligation to use the CP. Assessment and evaluation will be performed at the Committee for Medicinal Products for Human Use (CHMP) at EMA. If necessary, the evaluation will be supported by the HMPC. Nevertheless, the adoption is the responsibility of the CHMP, and the marketing authorization will be released by the European Commission.

If there is an intention to use the option to apply for registration as a traditional herbal medicinal product, the initial step is to check whether the product complies with the basic inclusion criteria. Basically, registration is open to combination products, but active substances derived from animal origin cannot be included. Under defined circumstances, even vitamins and/or minerals may be included if there are no safety concerns and the traditional use of the combination can be substantiated.

The indications that are suitable for registration as traditional herbal medicinal products in the EU are rather limited because the legislation excludes the need for prescription, supervision, or monitoring by a medical doctor. Below, the therapeutic areas of major importance for traditional herbal medicinal products registered in the EU are listed [6], along with examples of indications that have been granted:

- **Cough and cold.** Traditional herbal medicinal product used as an expectorant in cough associated with cold.
- **Mental stress and mood disorders.** Traditional herbal medicinal product for relief of mild symptoms of stress.

Table 5
Herbal drugs from TCM included in the *European Pharmacopoeia* (Section 5.22 of the *European Pharmacopoeia* provides the Chinese names as well) [8].

Latin name	English name	Monograph number
Acanthopanacis gracilistyli cortex	Acanthopanax bark	2432
Akebiae caulis	Akebia stem	2472
Amomi fructus	Amomum fruit	2554
Amomi fructus rotundus	Round amomum fruit	2555
Andrographidis herba	Andrographis herb	2712
Anemarrhenae asphodeloides rhizoma	Anemarrhena asphodeloides rhizome	2661
Angelicae dahuricae radix	Angelica dahurica root	2556
Angelicae pubescentis radix	Angelica pubescens root	2557
Angelicae sinensis radix	Angelica sinensis root	2558
Astragali mongholici radix	Astragalus mongholicus root	2435
Atractylodis lanceae rhizoma	Atractylodes lancea rhizome	2559
Atractylodis macrocephalae rhizoma	Atractylodes rhizome, largehead	2560
Aucklandiae radix	Aucklandia root	1797
Belamcandae chinensis rhizoma	Belamcanda chinensis rhizome	2561
Bistortae rhizoma	Bistort rhizome	2384
Bupleuri radix	Bupleurum root	2562
Carthami flos	Safflower flower	2386
Citri reticulatae epicarpium et mesocarpium	Mandarin epicarp and mesocarp	2430
Clematidis armandii caulis	Clematis armandii stem	2463
Codonopsidis radix	Codonopsis root	2714
Coicis semen	Coix seed	2454
Coptidis rhizoma	Chinese goldthread rhizome	2715
Dioscoreae nipponicae rhizoma	Dioscorea nipponica rhizome	2890
Dioscoreae oppositifoliae rhizoma	Dioscorea oppositifolia rhizome	2473
Drynariae rhizoma	Drynaria rhizome	2563
Ecliptae herba	Eclipta herb	2564
Ephedrae herba	Ephedra herb	2451
Eucommiae cortex	Eucommia bark	2412
Evodiae fructus	Evodia fruit	2718
Fraxini rhynchophyllae cortex	Fraxinus rhynchophylla bark	2452
Gardeniae fructus	Cape jasmine fruit	2565
Houttuyniae herba	Houttuynia herb	2722
Isatidis radix	Isatis root	2566
Ligustici chuanxiong rhizoma	Szechwan lovage rhizome	2634
Lycii fructus	Barbary wolfberry fruit	2612
Lycopi herba	Lycopus lucidus herb	2723
Magnoliae biondii flos immaturus	Magnolia biondii flower bud	2742
Magnoliae officinalis cortex	Magnolia officinalis bark	2567
Magnoliae officinalis flos	Magnolia officinalis flower	2568
Moutan cortex	Moutan bark	2474
Notoginseng radix	Notoginseng root	2383
Paeoniae radix alba	Peony root, white	2424
Paeoniae radix rubra	Peony root, red	2425
Persicariae tinctoriae folium	Indigo plant leaf	2727
Piperis fructus	Pepper	2477
Piperis longi fructus	Long pepper	2453
Platycodonis radix	Platycodon root	2660
Polygoni cuspidati rhizoma et radix	Polygonum cuspidatum rhizome and root	2724
Polygoni multiflori radix	Fleeceflower root	2433
Polygoni orientalis fructus	Polygonum orientale fruit	2726
Poria	Poria	2475
Prunellae spica	Common selfheal fruit-spike	2439
Puerariae lobatae radix	Kudzuvine root	2434
Puerariae thomsonii radix	Thomson kudzuvine root	2483
Salviae miltiorrhizae radix et rhizoma	Salvia miltiorrhiza root and rhizome	2663
Sanguisorbae radix	Sanguisorba root	2385
Schisandrae chinensis fructus	Schisandra fruit	2428
Scutellariae baicalensis radix	Baical skullcap root	2438
Sinomenii caulis	Orientvine stem	2450
Sophorae japonicae flos	Sophora flower	2639
Sophorae japonicae flos immaturus	Sophora flower bud	2427
Stephaniae tetrandrae radix	Fourstamen stephania root	2478
Uncariae rhynchophyllae ramulus cum uncis	Uncaria stem with hooks	2729
Zanthoxyli bungeani pericarpium	Zanthoxylum bungeanum pericarp	2656

- **Gastrointestinal disorders.** Traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion).
- **Urinary tract and gynecology disorders.** ① Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints; and ② traditional herbal

medicinal product for the symptomatic treatment of minor spasm associated with menstrual periods.

- **Sleep disorders and temporary insomnia.** Traditional herbal medicinal product for relief of mild symptoms of stress and to aid sleep.
- **Pain and inflammation.** Traditional herbal medicinal product for the prophylaxis of migraine headaches after serious conditions have been excluded by a medical doctor
- **Skin disorders and minor wounds.** Traditional herbal medicinal product used for the symptomatic relief of minor sprains and bruises.
- **Fatigue and weakness.** Traditional herbal medicinal product for temporary relief of symptoms of stress, such as fatigue and sensation of weakness.
- **Venous circulatory disorders.** Traditional herbal medicinal product to relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances.
- **Loss of appetite.** Traditional herbal medicinal product for temporary loss of appetite.

If there is a TCM product that complies with the requirements described above, it is necessary to demonstrate at least 15 years of medicinal use in China and at least 15 years of medicinal use in the EU. This requirement is linked to a specific active substance or a specific combination, and the medicinal use must be associated with a defined posology. The tradition should be sufficient to demonstrate absolutely safe use. If a product contains strongly acting alkaloids or cardio-active glycosides, there may be a major concern regarding the overall safety.

Quality is an essential requirement to guarantee wise usage of any medicinal product. Therefore, the requirements of herbal medicinal products and traditional herbal medicinal products are identical. Quality is already defined at the level of the starting material. Exact botanical identification is as important as a detailed description of processing and manufacturing. Regional nomenclature, substitutions, and chemo-varieties should be taken into account.

The key steps mentioned may be helpful for planning and consideration during the very early stages of product development. In order to achieve progress and proceed to the development of a dossier, the project should be supported by competent partners in Europe (e.g., partners in industry or consultants). The most valuable and essential recommendation is to consider scientific advice either by national authorities or at the level of the EMA (HMPC or CHMP). Scientific advice is available at any step of product development, and earlier is better for the applicant. The fees are reasonable, questions can address particular procedural or scientific issues, and the results are documented through a confidential protocol. Scientific advice may also be useful to elaborate major challenges in an early stage in order to allow wise decisions to be made about investments related to a project. In appropriate settings, scientific advice will substantially increase the chance of being successful.

6. Regulation and availability of traditional medicines at a global level

6.1. Convergence of regulatory systems

Global regulatory frameworks on herbal medicines and traditional medicines have been developed [12,13]. There is a common understanding of all concepts to assure quality, efficacy, and safety. Enforcement may vary in particular fields, such as classification, authorization procedures, requirements, life-cycle management, pharmacovigilance, labeling, and public information. Despite this diversity in environments, it should be noted that a global market for herbal and traditional medicines (or similar products with alternative classification) already exists.

The regulation of herbal and traditional medicines doubtless has the overall objective of safeguarding public health. The assessment of these products is science driven. Consequently, given the objectives and methodology, there is an option to strive for a common practice. Of course, it is not realistic to start thinking about worldwide identical legislation. Nevertheless, a stepwise improvement is realistic and may offer mid- and long-term perspectives to identify adequate practices and save resources. With respect to quality, there is a certain trend to strive for convergence of standards. This can be derived from the standards of Pharmacopoeias and from institutional harmonization of quality requirements, such as by the International Conference on Harmonization. Driven by the continuous development of guidelines and methodology in toxicology, there are similar requirements in preclinical investigations. The transfer of efficacy and therapeutic settings is the most challenging obstacle in the globalization of traditional therapeutic systems. Holistic therapeutic approaches cannot be reduced to medicinal products alone. Therefore, there must be a link to the qualification and education of healthcare professionals, and to the inclusion of accompanying therapeutic measurements.

If there is a road map to streamline different regulatory frameworks, it will include mutual understanding and knowledge about divergent requirements. Irrespective of divergent requirements, there is a common expectation to set parameters that ensure the quality, safety, and efficacy of herbal and traditional medicines. It is essential to provide adequate scientific data. The availability of scientific data will set the stage for better understanding and mutual acceptance of knowledge of herbal and traditional medicines.

6.2. Multinational networks

On a global scale, a harmonized regulatory approach applying a unique best practice and mutual acceptance is an extraordinary challenge. However, there are already regional regulatory networks between selected authorities, which have been established on different continents, such as Europe, Asia, and South America. The regulatory network within the EU based on a common legal framework may be the most advanced system with respect to multilateral acceptance. The ASEAN member countries have built an agreement on traditional medicines and health supplements. A global platform for communication among regulatory agencies is provided under the coordination of WHO by the International Regulatory Cooperation for Herbal Medicines (IRCH) [5]. Its mission is to protect and promote public health and safety through improved regulation for herbal medicines. Regulatory authorities from countries with a strong interest in herbal and traditional medicines are members that actively support the IRCH (e.g., Brazil, China, Germany, India, Japan, and South Africa). Thus, in the regulatory field, suitable multinational and global networks have already been initiated. There is a need for dialog between regulation and the scientific community. A convergence of regulatory requirements will contribute to the work-sharing of regulatory agencies, and will increase the availability of adequately assessed herbal and traditional medicinal products.

6.3. New methodology

New methodology is another key element with respect to the globalization of herbal medicines and traditional medicines. Scientists will obtain better insight into the mode of action, new data on safety and efficacy will be generated, and complementary methods will be available to guarantee quality control from harvest to application, including the complete value chain. There are still

major gaps in the available data and knowledge about herbal medicines and traditional medicines. Major incentives to generate additional knowledge and to close these gaps are limited. Science should address questions such as: What is the appropriate bioavailability of multi-component mixtures, which spectrum of targets is addressed, and what is the real impact of synergism? "Omics" technologies, such as metabolomics, transcriptomics, and proteomics are on the cusp of offering new dimensions in research [14]. Future challenges will be to apply new technologies to herbal and traditional medicines, and to step into a new dimension of data handling and understanding of complex networks. The new methodology should improve the options for assessment of herbal medicines and traditional medicines. An early dialog between regulation and the scientific community may speed up this process.

7. Conclusions

In the EU, a harmonized legal framework has been established to assure citizens access to herbal and traditional medicinal products with appropriate quality, safety, and efficacy. A defined set of procedures is offered in order to allow pharmaceutical companies to obtain access to the market.

The set of EU herbal monographs on herbal substances and preparations derived thereof is defining a unique standard. It is an excellent model of multinational harmonization of scientific assessment among a large set of countries with different cultural and social backgrounds in the application of traditional medicines. The establishment of EU herbal monographs is a transparent and open process that takes into account input from the scientific community and interested parties. The quality requirements defined by the *European Pharmacopoeia* and the EU monographs of the HMPC provide a full set of standards for herbal and traditional medicinal products on the market.

Globalization is affecting the market within the EU. European herbal medicinal products have been exported worldwide, and vice versa: herbal and traditional medicines from other parts of the world have been brought to the EU. The regulatory framework in the EU has been demonstrated to be applicable to allow herbal and traditional medicines from TCM access to the EU market. Moreover, guidance documents have been provided by the HMPC and pilot projects on monographs on the safety and efficacy of Chinese herbal drugs. In the *European Pharmacopoeia*, the number of quality monographs on herbal drugs with an origin in TCM is continuously increasing.

The scientific community should increase current knowledge with research initiatives including new methodology and technology. Better knowledge about multi-target modes of action, synergies and interactions, and availability in the human body will be a precondition for the future use of traditional and herbal medicinal products. Regulators should contribute to communication with the scientific community and industry. Stepwise convergence of regulatory requirements will improve the availability of herbal and traditional medicines to patients all over the world.

Compliance with ethics guidelines

Werner Knoess and Jacqueline Wiesner declare that they have no conflict of interest or financial conflicts to disclose.

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