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Current Status and Future Perspective in the Globalization of Traditional Chinese Medicines

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ABSTRACT

Globalization of traditional Chinese medicines started around 1996, which was initiated by the Chinese government. However, substantial progress was only achieved in recent years including the adoption of TCM quality monographs in the western pharmacopoeias (United States Pharmacopoeia and European Pharmacopoeia) and registration in main stream drug regulatory agencies such as US Food and Drug Administration (FDA) and European Medicines Agency (EMA). So far, several TCM herbal quality monographs were adopted by the United States Pharmacopoeia including Chinese Salvia, Ganoderma lucidum and Panax notoginseng, etc. Over 45 TCM quality monographs were recorded in the European Pharmacopoeia with 20 more in progress. After the successful registration of the first TCM product named Diao Xin Xue Kang as traditional medicine via the Medicines Evaluation Board of the Netherlands, several other TCM herbal products are in the registration process in several European member states. So far, there has been still not any TCM product authorized as a drug by the FDA regardless of a few TCM products in phase III or phase II clinical trials. This review summarizes the progress made in the globalization of traditional Chinese medicines in recent years and future issues in this regard.

Key words: Globalization, Traditional Chinese Medicine (TCM), Quality Monograph, Registration regulation

INTRODUCTION

TCM globalization, in a narrow sense, refers to the successful registration of TCM products as prescription drugs in the drug regulatory agencies of countries with western medicines as the main stream medical system, such as Unites States, Europe, and other countries. In a broad sense, it is the acceptance and integration of Chinese medical philosophy for health promotion and is the use of the Chinese medicinal concept for exercise, life style, prevention and treatment of disease including the wide use of raw materials, slices, extracts, and preparations as the drugs, alternative medicines, dietary supplements, healthy products or even as foods in countries outside of China. Over the past thirty years, China has significantly improved the TCM medicines development environment by a series of policies for the new drug approval. The evaluation and registration of TCM medicines in China was gradually developed in accordance with international standards[1]. However, it is a pity situation that no TCM products have been successfully marketed as the prescription drugs in the main stream medicine markets. Therefore, future efforts should focus on the successful marketing authorizations of TCM products in Food and Drug Administration (FDA) or European Medicine Agency (EMA) of the European Union (EU), enable the TCM theory, efficacy, and quality to be universally recognized by the international society, fulfill the zero breakthrough in entering the mainstream drug market of TCM proprietary products, and thereby lay a solid foundation for the TCM globalization.

THE MAIN PROGRESS IN TCM GLOBALIZATION

1. General registration situation of botanicals at the FDA

In 2004, the FDA issued the first authoritive guideline related to botanical products named "Guidance for Industry: Botanical Drug Products", which indicated the gradual exposure of botanical products in the market and also the increasing recognition of herbal medicines in the United States. Two years later, the approval of Veregen^{TM} by the FDA as a drug[2], hallmarked the herbal medicines to enter a new era which ended the time that botanicals can only be used as foods or dietary supplements to benefit the human health. With ten-year practice of the guideline and experience with two approved botanical drugs, Veregen and Fulyzaq, the FDA has almost finished the final revision of the new guideline for the registration of botanical drugs, which is expected to be released in early 2015.

Over the past ten years, there are over 600 herbal products applications for FDA registration under different stages. The number of botanical applications kept about constant up to 2012, but remarkably increased in 2013. These filed botanicals covered different therapeutic classes including oncology, cardio-renal, rheumatological, analgesic, antiviral, anti-infective, endocrine, metabolic, neuropsychology, urologic, reproductive, gastroenterology, dermatological, dental, and many others (Resource from a lecture of 13th Annual Oxford International Conference on the Science and Regulation of Botanicals). Among these applications,

only one third is for commercial registration, the others are for investigational purposes. Composite formulae products accounted for one third of the total number of applications, while single herb-derived preparations occupied the majority. Most of these applications are under Phase II clinical trials, and only a few under Phase III. So far, only two botanical drugs were approved. The first is a green tea-derived product, named Veregen™, for topical use to treat genital and perianal warts (condyloma acuminatum)[3]. The second botanical drug called Fulyzaq (Crofelemer) was approved six years after Veregen approval in 2012. Differing from Veregen as a topical product, Fulyzaq is an oral sustained release tablet derived from the crude plant latex of *Croton lechleri* (Dragon's Blood) for the treatment of HIV related diarrhea[4].

2. Current status of TCM product registration in FDA

TCM has long been used in China under the guidance of Chinese medical theory, which is very different from other traditional medicine or herbal medicine systems in the clinical practice. However, in terms of essence of drugs used for the treatment of diseases, TCM products should be no different from other herbal or botanical drugs, which ought to meet the requirements for safety, efficacy, and quality. Up to date, in total nine TCM products have been registered in FDA to conduct clinical trials (Table), named as Dantonic Pill, Ginkgo Tablet, KYG0395, Fuzhenghuayu Tablet, Xuezhikang Capsule, Weimaining Capsule, Kanglaite Injection, Kanglaite Soft Capsule and HMPL-004 covering for the treatment of cardiovascular, cancer, and inflammation diseases. The Dantonic pill, sponsored by Tasly Pharma Group, is the only TCM product under phase III clinical trial. During the process of phase III clinical trials, some other key issues need to be fully addressed, including chemical manufacture and control (CMC), pharmacology/toxicology, data processing, risk assessment, production in North America, etc. It is clear that there are still many hurdles to overcome before successful registration of TCM products as drugs in FDA.

3. General registration status of herbal medicines in Europe

The European herbal medicine registration regulations are mainly dominated by the European Medicines Agency (EMA)[5]. The registration of herbal medicines in Europe is mainly regulated by two directives numbered 2001/83/EC and 2004/24/EC. The 2001/83/EC was enacted in November of 2001 relating to the regulatory requirements for registering drugs in Europe, and represents the European prevailing basic drug regulations. 2004/24/EC is a supplementary revision regulation focusing on the simplified registration application for traditional herbal medicines which is commonly known as the traditional herbal medicine legislation for Europe[5, 6]. Based on the EU registration regulations, the herbal medicines in the European market can be classified into three categories. Class I is the traditional use (TU), which allows for simple registration application via centralized procedure or via national authorities in EU with provision limited to sufficient safety data and general efficacy in reference to 2004/24/EC. Class II refers to well-established use (WEU), requiring scientific literature demonstration that the bioactive ingredients have been used for the diseases for more than ten years with recognized efficacy and accepted safety. Registration of Class II herbal medicines can be applied in either a member country or directly to EMA following 2001/83/EC in a simple manner. Class III refers to the herbal medicines that pass all the drug registration procedure (full marketing authorization), during which the pharmaceutical enterprises need provide entire experimental together with literature data concerning the safety and efficacy. Registration of Class III herbal medicines can be applied in either a member country or directly to EMA via a centralized procedure with a full set of registration data also following 2001/83/EC. Due to the fact that the majority of TCM products has great difficulty to meet the requirements for Class III, or even Class II, the 2004/24/EC directive is the most feasible approach for TCM products to be registered in Europe and hence aroused a particular attention from the Chinese TCM pharmaceutical

Table Summary of the nine TCM products filed for application in FDA from China

Name	Indication	Clinical Trials.gov Identifier[a]	Clinical Phase in USA	Manufacture
Dantonic	Angina pectoris	NCT01659580	Phase III	Tasly Pharmaceuticals, Inc
Ginkgonin	Coronary heart disease; Angina pectoris	—[b]	Phase III	Shanhai Xingling Sci & Tech Pharmaceutical Co., Ltd
KYG0395	Primary Dysmenorrhea	NCT01588236	Phase II	Jiangsu Kanion Pharmaceutical Co.,Ltd
Fuzheng Huayu Tablet	Chronic Hepatitis Infection	NCT00854087	Phase II	Shanghai University of TCM & Shanghai Sundise Traditional Chinese Medicine Co., Ltd.
XueZhiKang Capsule	Hyperlipidemia	NCT01327014	Phase II	Beijing Peking University WBL Biotech Co., Ltd
WeiMaiNing	Lung cancer	—[b]	Phase II	Huayi Pharmaceutical Co., Ltd
Kanglaite Injection	Stage IV NSCLC	NCT01640730	Phase II	Kang Lai Te USA
Kanglaite Gelcap	Prostate Cancer	NCT01483586	Phase II	Kang Lai Te USA
HMPL-004	Ulcerative Colitis	NCT01882764 NCT01805791	Phase III	Hutchison Whampoa Limited

[a] Data are available from http://clinicaltrials.gov/.
[b] Data are not available from http://clinicaltrials.gov/.

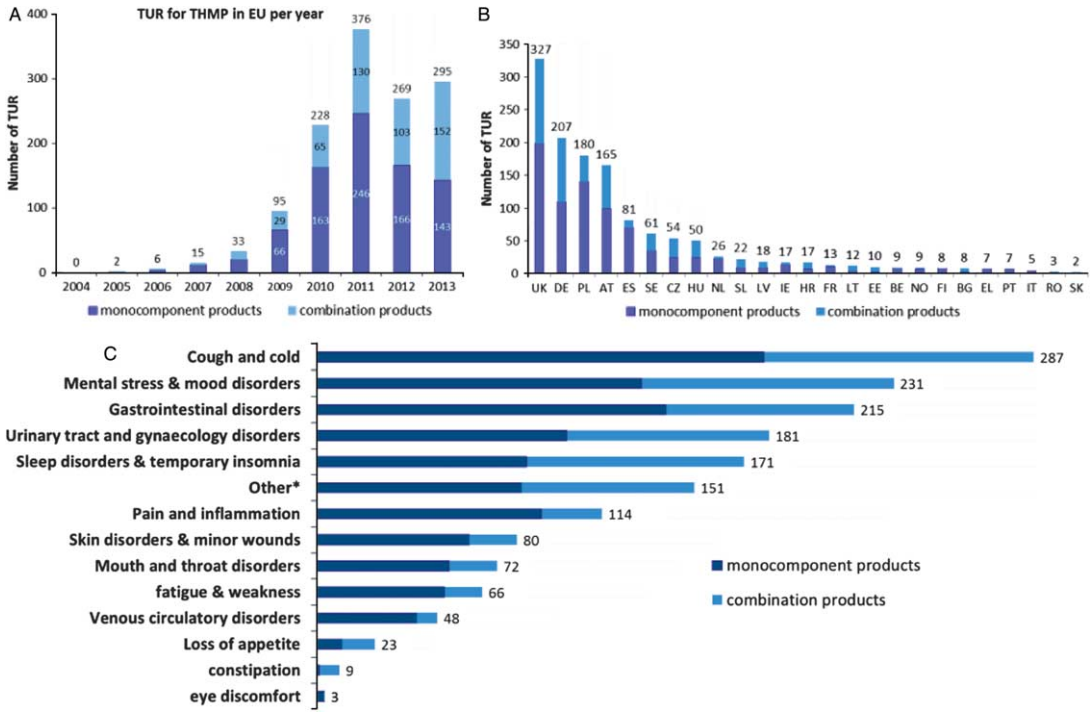

Figure Herbal applications in Europe by year (A), country (B) and therapeutic class (C).

companies[7]. In March 2012, Diao Xin Xue Kang Capsule was successfully approved by the Dutch Medicines Evaluation Board (MEB) with a simplified registration procedure following 2004/24/EC, which was the first and so far only registered TCM product as medicine in Europe[8, 9].

The 2004/24/EC directive mainly deals with the registration application of currently available traditional herbal medicines, rather than newly-developed herbal medicinal products. Since its implementation in 2004, 2004/24/EC has passed its seven year transition period on April 30, 2011[10]. From that time on, it is required that all herbal medicinal products in the European market have to be registered under the guidance of the 2004/24/EC directive.

4. Current status of TCM product registration in Europe

Since the implementation of 2004/24/EC, other than Diao Xin Xue Kang Capsule, other a few TCM products including Concentrated Danggui Pill (Lanzhou Foci Pharmaceutical Co. Ltd), Ginkgo Leaf Tablet (Yangtze River Pharmaceutical Group), and Danshen Tablet (Tasly Holding Group), are now in the process of registration following this directive in the different European member states. However, the number of herbal products with traditional use registration within Europe showed an obvious yearly increase, much more than the number of Class II and III applications. It is estimated that in total 1300 plus herbal products were registered with the simplified procedure from the implementation in 2004 till December of 2013 (Fig. A). Among all the European member states, United Kingdom, Denmark and Poland ranked in the top three countries with traditional use registered herbal products (Fig. B). The following ten herbs occupied the top ten for their derived herbal products with this simplified registration: Pelargonii Radix, Harpagophyti Radix, Valerianae Radix, Hyperici Herba, Passiflorae Herba, Ginseng Radix, Salviae Officinalis Folium, Thymi Herba, Echinaceae Purpureae Radix, and Hippocastani Semen. These herbal medicinal products are mainly used for the treatment of cold cough, regulating mind and emotion, and gastrointestinal disorders (Fig. C)[11].

KEY ISSUES IN TCM GLOBALIZATION

Despite the fact that the Chinese government launched the program of TCM globalization in the late nineties, TCM globalization progressed in a fairly slow pace, especially in terms of marketing authorization. This might attribute to the following three aspects.

1. Insufficient research and difficult to explain the TCM theory

Owing to the unique oriental philosophical features and extreme complexity, TCM theory can hardly be explained and approached by modern scientific methodologies. Hence, for western colleagues, the theory and its background are almost impossible to be understood. In addition, solid and reliable TCM research on the safety, quality and clinical efficacy is also fragile, which results in difficulties to meet the technical requirements of FDA and EMA or other regulatory sectors. Therefore, the registration of TCM herbal products with a long-term clinical practice in China becomes a highly difficult and even unpractical matter in FDA and EMA.

2. Deficient national integrated strategy

The current awkward status in registration of TCM products in Europe indicated that TCM globalization requires an integrated plan and strategy by a joint effort from Chinese government, pharmaceutical industry and scientific community. Due to the

insufficiency in realizing the actual difficulty, weak financial power and research capacity, pharmaceutical companies are not able to fulfill the TCM globalization registration soly through their own effort. It is now clear that TCM globalization will not achieve any breakthrough unless a whole-hearted cooperation among the government, industry and scientific community with a coordinated, integrated strategic plan is formulated.

3. Insufficient coordination and communication

Another major reason for the slow process in TCM global registration is the lack of sufficient coordination and communication with the European, American or other major regulatory agencies. On one hand, European and American experts have little knowledge, relevant experience or understanding of TCM; on the other hand, the Chinese scientists or entrepreneurs have not fully understood the regulatory requirements or guidelines released by FDA, EMA or other related agencies. This resulted in the detours and difficulties to meet the requirements in a precise and rapid manner. Therefore, this is a need to further strengthen the communications and exchanges with the scientists and regulatory officials in the intended communities to increase the understanding in mutual requirements and needs, which will faciliate to achieve the objective.

FUTURE PERSPECTIVES IN TCM GLOBALIZATION

For TCM globalization, the most important issue is to strengthen TCM itself, which turns it into an evidence-based medicine from its original experienced- or observational-feature. As TCM is a practice based medicine with a holistic view of the human body, the integrated research such as systems biology may function as a scientific bridge for Chinese and western medicine. Therefore, to promote scientific research using systems approach towards the understanding of TCM will be proposed.

The reliable and convincing evidence on the safety, efficacy and quality of traditional Chinese medicines, the so-called three golden criteria, have to be provided prior to its application for full marketing authorization. TCM basic research should be reinforced by means of the modern scientific and technological approaches for such aspects as the chemical composition, active principles, pharmacodynamics, pharmacokinetics, toxicology, phytochemical profiling, quality assay methods, etc. Based on the above research results, the *in vivo* ADME parameters and action mechanism should also be approached so as to develop the modernized TCM products that should possess the confirmed efficacy, scientific and feasible quality standard, proved safety, and clarified mechanism of action.

Another key issue in the viewpoint of national strategy, the Chinese central government should give an overall consideration to come out with a strategic plan and specific fund should be allocated to support the research works related to the global registration of TCM products with a long clinical practice and unique therapeutic properties.

Moreover, in the process of TCM modernization and globalization, harmonization of quality monographs in different pharmacopoeias or standard-setting organizations, such as ChP, USP, EP, ISO, WHO, etc. is also a challenging task. A modern annotation of TCM theory in a scientific language rather than philosophical or empirical, that makes it to be universally accepted by the modern scientific community should be one of the important future endeavours. Chinese government should provide structurally scientific support for building up USA and EU Community herbal monographs for herbs derived from TCM.

Some other key issues to hinder the TCM modernization and globalization should also be tackled. Governmental, industrial and academic alliance should be established to work together in a joint manner to increase the communication and collaboration among the domestic and international parties. It is believed that TCM globalization and successful international marketing authorization would be achievable in the foreseeable future.

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