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Review Article

Chinese Traditional Medicines Face Crucial Challenges in the New Regulatory Science: Approval and Reflection on Chinese Herbal Medicines

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Abstract: Traditional herbal formulae and conventional plant medicines have been recognized as "new" drugs approved in China and the complementary therapeutics appreciated in the West. With over 2,000 years evidence-based implementation in China, traditional plant medicines have showcased incredible modernized botanical drug development, but have not been accepted by international main stream medical markets due to the different understanding of traditional Chinese medicine (TCM). This article analyzed and reviewed the SFDA regulations, international general requirements, and crucial challenges when Chinese traditional drugs are registered. In addition, the constructive suggestions were outlined to advance the development of traditional plant medicines. Traditional plant medicines are facing the crucial challenges in these areas when registered and approved as modern drugs. New research ideas and strategies must be put forward and carried out if traditional plant medicines are extensively accepted by international main stream medical markets.
Keywords: Challenge; strategy; plant drug; regulation.

INTRODUCTION

Traditional Chinese herbs have been used clinically for several thousand years in China, with the history of utilizing herbs dating back to Spring and Autumn Period (BC 770-221) [1]. Before the introduction of Western medicine in China, Chinese medicine had been a mainstream. Even experienced a quite long period of war and famine, the population in China still reached 340 million when the collapse of the Qing Dynasty (1911) came. It indicated that the scattered traditional Chinese medicine had played an important role in improving people's health before the government-led health care system was established. Since the first modern drug named ephedrine isolated from Herba Ephedrae was identified and recognized by Western medicine [2], the research of traditional Chinese medicines becomes one of the important fields gradually in the process of new drug discovery and development. Chinese government has embraced some success by implementing the unique health care system of integrating Chinese Medicine into Western Medicine. Due to the discovery of artemisinin (a new generation of antimalarial drugs) from a traditional Chinese herb named Artemisia annua, Professor Yo-Yo Tu received the Lasker Award in September 2011, which is sometimes referred to as "America's Nobel". The achievement has far-reaching historical significance in research and development of Chinese medicines. But nowadays Chinese traditional medicines are facing crucial challenges in some areas: a) different substance foundations between traditional methodologies and modern manufacturing process; b) personalized solutions in herbal therapeutics versus the western pharmaceutical regimen of treatment in a specific population; c) different criteria on effectiveness and validation; d) manufacturing processing and industrial quality control. Therefore SFDA will strengthen the policy revision to adapt to the international general technical requirements in the next decade.

Regulatory Framework

Law

Article 3 from "Drug Administration Law of the People's Republic of China", which was revised in 2001, stipulates that "the nation promotes the development of modern medicine and traditional

medicine so that they will fully play its role in disease prevention, treatment and patient care."

Administrative regulations

On September 15, 2002, the "Regulations for Implementation of the Drug Administration Law of the People's Republic of China" was promulgated, and the management thinking of approval number, GAP and packaging labels for Chinese herbal medications, etc. were provided in articles 9, 40, 45, 71.

Departmental rules and regulations

On July 10, 2007, the newly revised "Administrative Measures of Drug Registration" confirmed that the categories for drug registration in China include traditional Chinese medicines (natural medicines), chemical drugs and biological products. The classification of registration and requirements for data submission of traditional Chinese medicines and natural medicinal products were specified in Appendix I, which were classified into 9 categories as follows [3].

- Active ingredients and their preparations extracted from plants, animals, minerals or other substances which have not been marketed in China.
- Newly discovered crude drugs and their preparations.
- New substitutes to existing Chinese crude drugs.
- New medicinal parts of existing crude drugs or their preparations.
- Active fractions and their preparations extracted from plants, animals, minerals or other substances which have not been marketed in China.
- Preparations of Chinese medicines and natural medicinal compounds, which have not been marketed in China.
    - TCM combination preparations.
    - Natural medicinal combination preparations.
    - Combination preparations consisting Chinese medicines, natural medicinal products and chemical drugs.
- Preparation with altered mode of drug delivery of marketed Chinese medicines and natural medicinal products.
- Preparation with altered dosage form of marketed Chinese medicines and natural medicinal products.
- Generics.

In January 2008, the State Food and Drug Administration (SFDA) issued the "Supplementary Regulations for Registration of Chinese Herb products," and then drafted "Guidelines for Natural Medicinal Research". For the first time, the regulations and technical requirements listed above clarified the different management ideas between traditional herbal medicines and modern herbal medicines.

Traditional plant medicines in China are formulated as the drugs that are applied clinically according to the traditional medical theories, most of which are used in the form of formulations, such as traditional Chinese drugs, Mongolian medicines, Tibetan medicines, and Uighur medicines. Modern plant medicines (natural medicines) are defined as the drugs used under the guidance of the modern medical theory, most of which are the medicinal preparations of extracts from single medicinal plant. The differences in registration laws and regulations between traditional plant medicines and modern plant medicines in China are shown in Table 1.

Evaluation team for plant medicines

In China, Center for Drug Evaluation (CDE) is in charge of the technical review of the registration of new herbal medicines. 28 people are engaged in the technical review of herbal medicines in CDE, who comprise the experts in pharmacology, pharmacology and toxicology, biostatistics, and medical professionals. Among them, the medical professionals assess if the formulation of plant medicines is guided by the traditional medicine theory. It is shown in Table 1 that the methods of research & development and evaluation standards of formulations are different from each other due to their guidance of different medical theories.

Evaluation and approval results of plant medicines in China Between 2006 and 2010

During the five years from 2006 to 2010, 181 plant medicines were approved to use clinically, nearly 94% of which are preparation of traditional formulations, and only 12 belong to modern plant drugs (including one imported plant drug). All of them are prepared from single medicinal plant (Table 2, Figure 1, 2). The indications of these drugs focus on the following disease areas, surgery, digestion, respiration, neurology, gynaecology and obstetrics, etc.

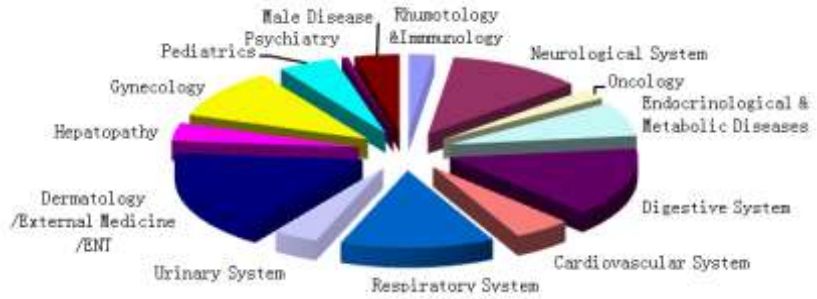

Fig. 1: The proportion of various diseases treated with approved herbal medicines from 2006 to 2010. Most new drugs accounting for 66% of total approved herbal-derived drugs were included in the respiratory, digestive, nervous, gynecology, skin, and topical agents.

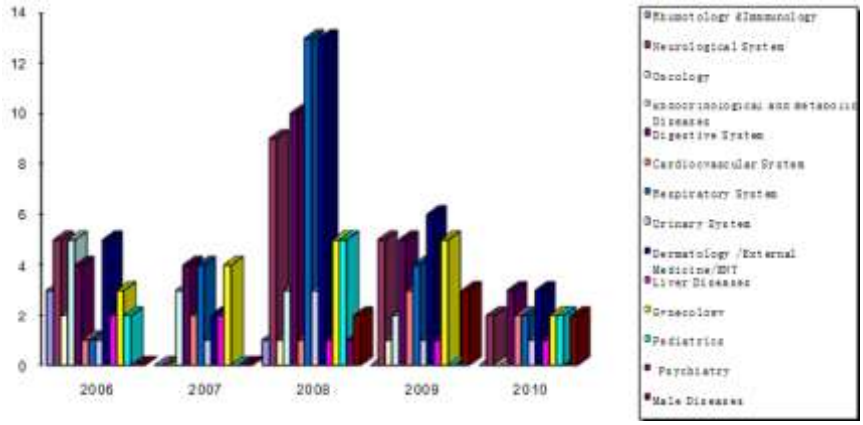

Fig. 2: The number of approved herbal medicines for the treatment of various diseases each year. The amount of new SFDA-approved drugs surged in 2008, which had a connection with concentrated cleaning up drug-review-lag at that time. The situation of approved drugs was relatively smooth in remaining 4 years

Challenges

Although many traditional plant medicines were approved to use clinically and incorporated into the national health insurance system in China, few approvals are accepted by Europe and North America. Traditional plant medicines still cannot enter the mainstream pharmaceutical markets of these countries, and are labeled as dietary supplements, nutrition supplements or over-the-counter medications. The different understanding of plant drug efficacy and safety caused this discordance due to the differences of the East-West culture and medical practice experience. Therefore, traditional Chinese medicines are actually facing seemingly scientific but unfair technical requirements and regulations under the modern framework of regulations for new drug development. According to the current international requirements, there exist the following challenges on the research and development of traditional Chinese medicines.

- The rationality studies on traditional Chinese medicines cannot be completely substituted by traditional technology and clinical experience.
- The flexibility of individual treatment is limited for the guidance of safety and effectiveness of treating large population with the same product.
- Different judgment standards of medicinal curative effect between the western and Chinese medicine result in inconsistence in evaluating the clinical value of new drugs.
- It is difficult that the quality of new herbal drugs is as stable as that of small molecule compounds, owing to the complex material base of plant medicines and limited measures of quality control.

Thoughts

The above mentioned challenges prompt China's regulatory agencies to ponder why no new botanical drugs possessing far-reaching significance have been discovered since artemisinin inception.

Research and development

- The research and development logic of traditional plant medicines is incompletely equal to that of modern botanical medicines. The transformation of these two logics is based on the correct understanding of traditional culture and judgment of traditional medical theories.
- The comprehensive and effective methods for product quality management should be

established to strengthen quality control of plant drugs.

- It is necessary to develop some new methods and technologies in order to overcome the difficulty in carrying out human PK / PD study of plant medicines
- The dummy technologies of plant medicines in clinical trials need to be explored.

Supervision and management

- The classification management of traditional plant medicines and modern botanical drugs is imperative.
- The industrialization process of plant medicines from natural resource may result in the secondary ecological issues, which need to be assessed.
- It is necessary to use multiple batches of samples for clinical trials and the quality control standards of future marketing products should be established on the basis of human test data.
- The evaluation methods for traditional plant medicine effectiveness should be developed.
- The adverse reactions surveillance and pharmacovigilance of plant drugs should be strengthened [4].

In recent years, modern medicine has transformed from the previous biomedical model to "bio-psycho-social medical model". The development of medicine has also made us gradually realize that the complexity of human disease is far more than the human science and technology progress. Therefore mainstream medicine, traditional medicine or alternative medicine has recognized the complementarities between each other nowadays.

Strategies

In 2006, Veregen, the first plant drug approved by US FDA, was put into market [5]. The approval caused a word-wide rethinking in terms of how to research and develop plant medicines. For the first time, the requirements for this type of drugs in CMC, mechanism of action, PK/PD and clinical trial are different from those for small molecule chemicals. China SFDA has adjusted regulations and strategies in due course for classification management of traditional and modern botanical drugs. The goals are:

- To speed up the transformation of traditional herbal medicine industry based on the development of traditional medicine and current medical system of integrated traditional Chinese and Western medicine;
- To gradually line with the international standards through the development of modern herbal medicines;
- To promote the transformation of some listed traditional herbal medicines to modern herbal drugs based on the large scale clinical trial data before and after listing;
- To explore the essential connection between the evaluation system of drug clinical effectiveness based on traditional medicine and benefits for patients.
- To grope for new plant medicine research and development models, such as development of multi-component Chinese medicines based on modern plant drugs, which are similar to compound preparations composed of small molecular compounds.

Currently, it is much more difficult to develop a new drug according to single-target action. Although advanced science and technology enables us can to understand disease from the protein and gene level, the number of global drugs approved is declining year by year. Plant medicines show great potential in developing new drugs due to their complicated ingredients and actions of multi-target and multi-route. Although still faced with many challenges, the traditional plant medicine holds great promise for extensive acceptance by people from different regions and cultural backgrounds, like acupuncture and taichi.

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Table 1 The differences in registration laws and regulations between traditional and modern plant medicines in China

Classification	Guidance for traditional medicine theory	Prescription	Preparation process	Route of administration	Daily dosage	Functions & Indications	Applicable population	Regulatory requirements	Key points for review
Traditional plant medicines	yes	From traditional recordation; still in clinical use today; non-toxic medicinal materials or incompatibility; has statutory standards of medicinal materials	Same as traditional process.	Same as traditional recordation	Same as traditional recordation	Same as traditional recordation & syndrome	Same as traditional recordation; elimination of pregnant women, infants & young children, and other specific populations	Non-clinical safety studies only; exemption from clinical trials	Safety
	yes	From traditional recordation or doctor clinical experience ; has clinical use experience in modern	Same as traditional process or use modern technology	Same as or different from traditional recordation	Same as traditional recordation or based on clinical experience	Same as traditional recordation & combination of disease and syndrome	Same as traditional recordation or has clinical use experience	Non-clinical studies, phases Ⅱ andⅢ clinical trials	Safety and effectiveness
Modern plant medicines	No	From laboratory screening	Use modern technology for extraction and purification	Vary with physical and chemical properties; mechanisms; pharmacological activities	PK / PD; dose screening	Disease	No specific requirements	Non-clinical studies, human PK trials and phases Ⅰ, Ⅱand Ⅲ clinical trials	Safety and effectiveness

Table 2: The number of approved plant medicines in China from 2006 to 2010

Herbal medicines	2006	2007	2008	2009	2010
Traditional Herbal medicines (THM)	30	20	65	38	17
Modern Herbal medicines (MHM)	4	2	2+1 (Imported medicine)	0	3

Table 3: The Differences between TCM, Alternative medicine and Western medicine

Medical system	Theoretical foundation	Practical foundation	Therapeutic principle	Treatment measures	Treatment outcome
TCM	Ancient Chinese Philosophy and whole concept	Empirical medicine	Balance	Chinese herbs, acupuncture, massage, cupping, bian stone, qigong, and others	Improved quality of life
Alternative medicine	Whole concept	Empirical medicine	Regulation	Homeopathy, diet therapy, naturopathy, spiritual idea therapy, energy therapy, physical therapy, and exercise therapy	Improved quality of life
Western medicine	Anatomy, physiology, and pathology	Lab-based medicine	Antagonism	Medication, radiation therapy, and surgery	Removal of diseased site