FEATURE ARTICLE

Status and Thoughts of Chinese Patent Medicines Seeking Approval in the US Market

LEI Xiang, CHEN Jing, LIU Chun-Xiang, LIN Jia, LOU Jing, and SHANG Hong-cai

ABSTRACT Veregên™ and Fulyzaq are the first two botanical drug products that were approved by the Food and Drug Administration (FDA) to market in the US. Additional herbal medicines, including Compound Danshen Dripping Pills (复方丹参滴丸), Fuzheng Huayu Tablets (扶正化瘀片), Xuezhi Kang Capsule (血脂康胶囊), Guizhi Fuling Capsule (桂枝茯苓胶囊), Kanglate Capsule (康莱特胶囊) and Kanglate Injection (康莱特注射液), have filed the investigational new drug (IND) application to the FDA and are in phase II or phase III clinical development. In order to gain better understanding of the process of botanical drug approval in the US, this article examines the aforementioned drugs by looking at their composition, indication, prior clinical experience and clinical development process, and summarizes key features that enabled IND filing and marketing approval by the FDA.

KEYWORDS Chinese medicine, botanical drug, Food and Drug Administration's review

In 1996, Ministry of Science and Technology of China and State Administration of Traditional Chinese Medicine of China proposed the Chinese medicine modernization development strategy, proposing that by year 2010 two to three herbal drugs be marketed in the US as new drug products (as opposed to dietary supplements).

In 2004, the US Food and Drug Administration (FDA) issued Guidance for Industry Botanical Drug Products, which outlined the regulatory requirements of botanical drug products for investigational new drug (IND) application and differentiated them from that of synthetic or highly purified drugs. Under this guidance, the FDA granted marketing approvals for Veregên™ and Fulyzaq in 2006 and 2012, respectively. A number of other Chinese patent medicines are being studied in clinical trials in anticipation of filing the new drug application (NDA) and obtaining approval from the FDA. In order to help the researchers and pharmaceutical enterprises better understand the application and approval process of Chinese patent medicines in the US, the authors took a closer look at the Chinese patent medicines that have been approved or are seeking FDA approval and provided our thoughts on the endeavor.

Two FDA-Approved Botanical Drugs

Veregên™ ointment is the first botanical drug approved by FDA. The approval is a milestone that marks the first herbal medicine as a regulated drug product entering the US market. Six years after the approval of Veregên™, Fulyzaq, the second botanical drug and first in oral preparation, was approved by FDA. The composition, indication and approval timeline of the two products are listed in Table 1. These approvals signify the agency’s recognition and acknowledgement of efficacy and safety of these botanical drug products and pave the way for research, development and marketing of botanical drugs.

In addition to those two approved products, a number of additional botanical drug products are in phase II or phase III clinical development. Their developer, target indication and development status are listed in Table 2. Their ingredients and therapeutic indications as marketed products in China are summarized in Table 3.

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Table 1. The Basic Information of Two FDA-Approved Botanical Drugs

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Ingredient</th>
<th>Indication</th>
<th>Route of administration</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veregen™</td>
<td>Sinecatachins; a variety of catechin ingredients and the mixture of other tea related substances</td>
<td>External genital and perianal warts in immunocompetent patients age 18 or older</td>
<td>Topical treatment</td>
<td>October 31, 2006</td>
</tr>
<tr>
<td>Fulyzaq™</td>
<td>Active ingredient crotalaria, Derived from the red sap of the Croton lechleri plant</td>
<td>Noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy</td>
<td>Oral</td>
<td>December 31, 2012</td>
</tr>
</tbody>
</table>

Note: HIV/AIDS: human immunodeficiency virus infection/acquired immunodeficiency syndrome

Table 2. Botanical Drugs in Clinical Development (IND Application to the FDA)

<table>
<thead>
<tr>
<th>Chinese drug name</th>
<th>Trial registered name</th>
<th>Developer</th>
<th>Indication</th>
<th>Phase II status</th>
<th>Latest status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound Danshen Dipping Pills (复方丹参滴丸)</td>
<td>Dantonic Capsule(R)/TF9(R)</td>
<td>Taish Pharmaceutical Group Co. Ltd.</td>
<td>Angina pectoris</td>
<td>Completed in 2010(R)</td>
<td>Phase III ongoing and expected to be completed by 2014(R)</td>
</tr>
<tr>
<td>Guizhi Fuling Capsule (桂枝茯苓丸)</td>
<td>Kanion Capsule(R)/KYG0395(R)</td>
<td>Jiangsu Kanion Pharmaceutical Co. Ltd.</td>
<td>Primary dysmenorrhea</td>
<td>The Phase IIa completed in 2009(R)</td>
<td>The Phase IIb initiated in 2012 and expected to be completed by 2014(R)</td>
</tr>
<tr>
<td>Fuzheng Huayu Tablets (扶正化瘀片)</td>
<td>Fuzheng Huayu(R)</td>
<td>Shanghai Huanghai Pharmaceutical Co. Ltd.</td>
<td>Hepatitis C-associated liver fibrosis</td>
<td>Completed in 2013</td>
<td>unknown</td>
</tr>
<tr>
<td>Xuezhikang Capsule (血栓通胶囊)</td>
<td>XueZhiKang (XZX)(R)</td>
<td>Beijing Beida Weixin Biological Technology Co. Ltd.</td>
<td>Hyperlipidemia</td>
<td>Completed in 2012</td>
<td>unknown</td>
</tr>
<tr>
<td>Kanglaite Capsule (康莱特胶囊)</td>
<td>Kanglaite Gelcap (KL,Tc)(R)</td>
<td>Zhejiang Kanglaite Pharmaceutical Co. Ltd.</td>
<td>Prostate cancer</td>
<td>ongoing</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kanglaite Injection (康莱特注射液)</td>
<td>Kanglaite Injection(R)/I</td>
<td>Zhejiang Kanglaite Pharmaceutical Co. Ltd.</td>
<td>Pancreatic cancer</td>
<td>ongoing</td>
<td>Unknown</td>
</tr>
<tr>
<td>Unknown</td>
<td>HMPL-004(R)/I</td>
<td>Hutchison Whampoa Pharmaceutical Co. Ltd.</td>
<td>Ulcerative colitis</td>
<td>Completed in 2009</td>
<td>Phase III has been initiate and expected to be completed by 2014(R)</td>
</tr>
<tr>
<td>Unknown</td>
<td>HMPL-004(R)/I</td>
<td>Hutchison Whampoa Pharmaceutical Co. Ltd.</td>
<td>Crohn’s disease</td>
<td>Completed in 2009</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 3. Ingredients and Indications as Marketed Products in China

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Ingredient</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound Danshen Dipping Pills</td>
<td>Radix Salviae Miltiorrhiae, Radix Notoginseng, Borneolum Syntheticum</td>
<td>Activating blood and resolve stasis, regulating qi-flowing for relieving pain. Indications for chest tightness and precordial tingling associated with angina pectoris due to qi stagnation and blood stasis.</td>
</tr>
<tr>
<td>Guizhi Fuling Capsule</td>
<td>Cinnamomum cassia Presl, Poria, Cortex Moutan, Semen Persicae, Radix Paeoniae Alba</td>
<td>Promoting blood circulation, removing blood stasis, eliminating mass. 1. Female concretion lumps due to static blood blocking collaterals, amenorrhea, dysmenorrhea, postpartum lochia endless. Uterine fibroids, chronic pelvic mass, dysmenorrhea, endometriosis and ovarian cysts. 2. Female breast cystic hyperplasia belonging to syndrome of collateral retardation due to blood stasis, syndrome of breast pain, breast lumps, and shortness of breath. 3. Prostatic hyperplasia belonging to syndrome of blood stasis obstructing the bladder, which has syndrome of urinary hesitancy, urinary retention and pelvic pain and distension.</td>
</tr>
<tr>
<td>Fuzheng Huayu Tablets (Capsule)</td>
<td>Radix Salviae Miltiorrhiae, fermented mycelium from Cordyceps Sinensis Powder, Semen Persicae, Pollen Pini, Herba Gynostemmae, Fructus Schisandrae Chinensis</td>
<td>Strengthening the essence and nourishing the Liver (Gan). For liver fibrosis in hepatitis B belonging to the syndrome of collateral retardation due to blood stasis and insufficiency of Liver and Kidney (Shen) essence and blood, which has the syndrome of hypochondriac pain, dim complexion, spider angioma, soreness and weakness of the waist and knees, fatigue, dizziness, dry eyes, dark-colored tongue with or without ecchymosis, wiry and thready pulse.</td>
</tr>
<tr>
<td>Xuezhikang Capsule</td>
<td>Fermentum Rubrum</td>
<td>Dehumidification expectorant, promoting blood circulation to remove blood stasis, reinforcing Spleen (Pi) to promote digestion. This product is used to treat shortness of breath, fatigue, dizziness, headache, chest tightness, bloating, poor appetite, indigestion due to Spleen deficiency phlegm silt block and hyperlipidemia. It is also used in adjuvant therapy for the treatment of cardiovascular and cerebrovascular diseases due to hyperlipidemia and atherosclerosis.</td>
</tr>
<tr>
<td>Kanglaite Capsule</td>
<td>Coix seed oil</td>
<td>Supplemeting qi and nourishing yin and eliminating mass. For preoperative and inoperable Spleen phlegm, qi and yin deficiency type of primary non-small cell lung cancer.</td>
</tr>
<tr>
<td>Kanglaite Capsule</td>
<td>Coiec oil injection</td>
<td>Supplemeting qi and nourishing yin and eliminating mass. For inoperable primary non-small cell lung cancer and hepatocellular carcinoma with the type of deficiency of both qi and yin as well as dampness obstructing Spleen-Stomach (Wei). It has synergistic effect to radiotherapy and chemotherapy, and has the effect of anti-evil pathogenic and analgesic effects for advanced lung cancer.</td>
</tr>
<tr>
<td>HMPL-004</td>
<td>Andrographis paniculata's components</td>
<td>No information</td>
</tr>
</tbody>
</table>
Characteristics of Chinese Patent Medicines under Evaluation by the FDA

The following features are identified that are common to the botanical drugs under evaluation by the FDA.

They are all well-known products in China. Except HMPL-004 not listed in China, the rest drugs had been marketed and are well-recognized in China. They also have a huge market share in China when compared with other Chinese medicines for the similar disease indications. Such wide usage of these products amounted to a large exposure population as well as well-characterized adverse effects. The information on the exposure, sales volume and adverse effects for prior market drugs are requested by the FDA when filing NDA as supporting evidence in evaluating the safety of the drug products. It is an advantage for prior marketed drugs to have these data that serve to strengthen the application.

Another advantage of these products is their simple formula. These Chinese patent medicines have only one (Xuezhikang Capsule, Kanglaite Capsule, Kanglaite Injection, HMPL-004) to six (Fuzheng Huayu Tablets) constituents. In comparison to multi-constituent herbal medicines, the chemistry, manufacture and controls (CMC) information required by the regulatory agency will be less cumbersome to generate.

In conjunction with the high market use, there have been a large number of prior studies on the marketed drug products. An estimate of 240 to 3,000 publications in China National Knowledge Infrastructure (CNKI) has been associated with each drug product that covers both pre-clinical and clinical studies as well as the characteristics of various aspects of the products. The literature will also be included in the NDA package and serve as supportive evidence for FDA's review.

Some Considerations of FDA’s Review and Approval of Chinese Patent Medicine
Selection of Target Diseases

Disease indication selection should be focused on diseases that have unmet medical need, i.e., no treatment or lack of effective treatment with Western medicines. For instance, treatment with Western medicine is not satisfactory for chronic diseases such as cardiovascular disease, type 2 diabetes, chronic pain and cancer; and botanical drugs in Chinese medicine can offer an effective option.

The indication for Fulyzaq is an excellent example. There was no FDA approved therapy for noninfectious diarrhea in human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) patients in the US. There was a clear unmet need for the indication. Per the FDA's Manuals of Policies and Procedures (MAPP 6020.3 Rev. 2), priority review designation is assigned to applications for drugs that treat serious conditions and provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies. Thus Fulyzaq application received FDA's priority review with shortened review timeline.

The selection of hepatitis C-associated liver cirrhosis as the target disease for Fuzheng Huayu Tablets is another example. There are about 170–200 million people who are infected with chronic hepatitis virus in the world, and 50 million in US. Chronic viral hepatitis is the main liver disease in the US that is associated with the direct medical costs up to $11 billion. Twenty percent of patients infected with hepatitis C will develop liver cirrhosis. Currently, there is no FDA-approved treatment for liver fibrosis.

Cancer is another indication with unmet medical need. There is no lack of effort in developing the treatment of cancer. Among the 34 new drugs approved by FDA in 2012, 13 were antineoplastic drugs. The target disease for Kanglaite Injection is pancreatic cancer, one of the leading causes of cancer-related deaths with poor prognosis and poor 5-year survival rate.

Selection of Botanical Drugs

Unlike synthetic or highly purified drugs, botanical drugs are derived from plants and are usually prepared as complex mixtures. Their chemical constituents are not always well defined chemically nor can be easily quantified. Although the guidance does not mandate the sponsor company of a botanical drug to identify the active constituents, for CMC information FDA may rely on a combination of tests and controls to ensure the identity, purity, quality, strength, potency, and consistency of botanical drugs.
It will be very challenging to develop these tests to determine these properties of botanical drugs with mixture of multiple ingredients, unclear or complex chemical composition. Inadequate tests and lack of characterization of the drug properties will certainly hinder the FDA review. Therefore, when seeking market approval in countries like US, selection of botanical drugs with simple and limited constituents would be preferred.

As described earlier, the compositions of the botanical drugs currently in development clinical are relatively simple, which allowed a smooth FDA review and easy transition into phase II clinical trials. For the two approved botanical drugs, the drug constituents are known and the active ingredients are well defined. These features likely played a favorable role in gaining the FDA's approval.

Selection of Route of Administration

The approval of the two botanical drugs, from a relatively low risk topical preparation at first to a more challenging oral formulation thereafter, indicated that the approval process was also a learning experience for FDA. In general, safety and tolerability of topical and oral preparations are relatively easy to control in comparison to injectable preparations. Among the seven botanical drugs that are being evaluated by the FDA, only Kanglaite Injection belongs to the injectable formulation while others are all oral preparations. However, Kanglaite Injection is composed of a single drug extract, which can be a plus as a botanical drug seeking the FDA approval.

Selection of Target Indication

A clearly defined clinical indication and a significant clinical benefit are key to obtaining FDA approval. As shown in Table 2, the existing prescribing information of these marketed drugs centers around improving the body functions and syndromes that are consistent with the theory of Chinese medicine. Not surprisingly, the target indications when applying for market approval in US need to be consistent with the disease definition in Western medicine. Typically a single disease indication is selected initially for one product when seeking approval, although more than one indication can be pursued sequentially or in parallel. Selecting the right indication requires careful evaluation of the drug's mechanism of action, preclinical evidence and clinical experience. Cost and duration of conducting clinical trials, and other business-related considerations are also factored in when making the decision.

After Guizhi Fuling Capsule obtaining the funding support, the sponsor of Guizhi Fuling Capsule, Kanion Pharmaceutical Co., spent 3 years to screen multiple gynecological diseases that the Guizhi Fuling Capsule can treat and chose the primary dysmenorrhea as the indication to file NDA with the FDA. At that time of the application, there was no therapy in Western medicine that was indicated for the treatment of patients with primary dysmenorrhea. For Compound Danshen Dropping Pills, two separate indications were filed with FDA, including the secondary prevention of repeated angina and the secondary prevention of serious cardiovascular events in patients with myocardial infarction. After careful evaluation of the market size, competing treatment options and other risk factors associated with the development, the former was chosen as the indication for clinical trials.

Collaboration and Outsourcing

Developing international cooperation is a necessary process to enter international market and obtain international approval. In preclinical studies, we can seek cooperation with foreign research institutions and co-publish academic papers to establish credibility and gain influence in the research community. In clinical studies, one should seek assistance of the local contract research organizations who are knowledgeable about local laws and regulations, and specialized in conducting clinical trials in the country. Almost all drugs listed in this article have established international cooperation. For example, the IND work of compoundDanshen Dropping Pills was done in collaboration with the Harvard School of Public Health, Harvard School of Medicine, and the US National Institutes of Health Alternative Medicine Center at Harvard University. The phase II clinical program of Xuezhikang Capsule was contracted to multiple well-established Contract Research Organization (CROs) companies on each concrete work. Fuzheng Huayu Tablets development was outsourced to a local CRO and an electronic data capture system was utilized to collect clinical trial data.

Non-Clinical Toxicology Studies

Per FDA’s Guidance, no new non-clinical toxicology studies are required in order to initiate the phase I and phase II clinical studies for marketed products as long as there have been no safety issues
and same doses as recommended are to be used. However, in the expanded phase III clinical trials, the non-clinical toxicology studies may be required similarly as for new molecular entities.

In recent years, there are up to 40 botanical drugs applied for IND annually and more than 85% of them obtained the IND, unfortunately not many drugs advanced to phase III clinical trials. Unable to satisfy the requirement of the non-clinical safety studies was considered part of the reason.\(^{(24)}\) The current drug registration management measures issued by China State Food and Drug Administration mandates almost all non-clinical safety studies as required by the FDA, but some early approved drugs pre-date the measures and the required non-clinical studies were not conducted. Lack of recognition of the study significance and inadequate case-specific study design are additional issues that need to be fixed.\(^{(25,26)}\) Obviously, to globalization the Chinese medicine and to penetrate the foreign markets, one must follow the rules and policies governed by the local regulatory agencies. This effort should be viewed not only as a path of getting marketing approval but also a process of re-development, re-invention and validation of marketed drugs.

**Conclusion**

There are more Chinese medicines than those listed here that have been granted the IND status by the FDA. It is encouraging to see that two botanical drugs have been approved and others are in phase II or phase III development. The advancement of these Chinese patent medicines on their way into the US market also signifies the FDA’s recognition and acceptance of therapies other than conventional synthetic small molecule drugs.

At least two categories of Chinese patent medicines are considered favorable in getting the US or other international market approval. Those in the first category have their efficacy demonstrated using the gold standard. For example, the effect of lipid-lowering drug, Xuezhi Kang Capsule, was demonstrated by quantifying the low density lipoprotein, an objective measure that was used for statins. Those in the second category are shown to be effective in the diseases that have high unmet medical need. An example of such drugs includes Fuzheng Huayu Capsule for the treatment of hepatitis C-associated liver fibrosis. In addition, successful execution of clinical development involves getting familiarized with the country’s regulation and guidelines, seeking experts’ advice on trial design and clinical development plan, outsourcing the work to CROs for trial implementation, monitoring, data management and medical writing as necessary. The overall drug development process is time-consuming and costly. Despite the success we had in getting Chinese patent medicines into the international market, one should not forget the challenges we are facing. The experience we obtained from the past development efforts should help us make bigger stride on this path.

**Conflict of Interests**

The authors have no conflict of interests to declare.

**Author Contributions**

Lei X wrote this article. Chen J, Liu CX, Lin J, and Lou J involved in data collecting and organizing. Shang HC guided the writing of this article, and made many valuable suggestions.

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9. ClinicalTrials.gov. Assess the anti-fibrotic activity of...


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