Developing Traditional Chinese Medicines as Botanical Drugs for the US Market

By Mukesh Kumar, PhD, RAC, and Hemant Jethwani, MS

Therapeutic products derived from medicinal plants have been used throughout the history of mankind. The use of herbs for treating a variety of ailments has been described in the oldest of human civilizations. Several modern drugs owe their origin to plants.[1] Some prominent examples are Tamiflu (based on the Chinese spice star anise), Atropine (plants of the *Solanaceae* family), Digoxin (Foxglove plant *Digitalis Lanata*) and Taxol (Pacific yew tree, *Taxus brevifolia*). While whole herbs have been used in various forms for medicinal purposes, extracts or partially purified components, called botanical drugs, have more commonly been used in herbal treatments. Botanical drugs differ from conventional drugs in that they comprise mixtures of multiple components whose therapeutic effects are not clearly defined. In many cultures, mainstream traditional therapies heavily rely upon treatment with botanical products. In the US, most botanicals are sold as dietary supplements.

Herbal treatments derived from traditional Chinese medicine (TCM) practices, although very popular and considered efficacious in their country of origin, are primarily sold either as ethnic food products or as dietary supplements in the US. No botanical products based on TCM have been approved by the US Food and Drug Administration (FDA) as therapeutic products due to lack of evidence for safety and efficacy as demonstrated by appropriately designed clinical trials. Also, there are unanswered questions about the manufacturing practices for these products and their mechanisms of action. This article discusses how a Chinese botanical product may be developed for marketing as a prescription drug in the US. These processes are similar to those required for approval by the European Medicines Agency (EMEA).

TCM in China and Taiwan

TCM has been used in China and Taiwan for thousands of years for diverse indications. TCM practices include herbal medicine, acupuncture, dietary therapy, and *Tui na* and *Shiatsu* massage. TCM aims to create overall well-being to prevent or cure diseases rather than taking a reactive approach by treating the symptoms of an ailment. It is based on the ancient Chinese perception of humans as microcosms of the larger, surrounding universe, interconnected with nature and subject to its forces. The human body is regarded as an organic entity in which the various organs, tissues and other parts have distinct functions but are all interdependent. In this view, health and disease relate to balance or imbalance of the functions. TCM emphasizes individualized treatment. Practitioners traditionally use four methods to evaluate a patient's condition: observing (especially the tongue), hearing/smelling, asking/interviewing and touching/palpating (especially the pulse). They may prescribe a combination of therapeutic measures, the most commonly being Chinese herbal medicine and acupuncture. The Chinese *materia medica* (a pharmacological reference book used by TCM practitioners) contains hundreds of medicinal substances—primarily plants, but also some minerals and animal products—classified by their perceived action in the body. Different parts of plants such as the leaves, roots, stems, flowers and seeds are used. Usually, herbs are combined in formulas and given as teas, capsules, tinctures or powders.

Diagnosis of diseases and administration of herbal drugs by TCM practitioners are vastly different from the approach of physicians trained in Western medicine. Therefore, it is difficult to consider these products as simple chemical or biological entities that can be prescribed by any physician.

Traditional herbal medicine is regulated in China and Taiwan by a process separate from that for chemical and biological drugs. The manufacturer of an herbal substance claims efficacy to treat an indication based on historical literature as defined in the five books in Chinese Classics Eastern Literature and must only meet the good manufacturing requirement as defined in Chinese regulations for TCM. The manufacturer is not required to prove safety due to the long history of human exposure. Over the last few years, the Chinese State Food and Drug Administration (SFDA) and the Taiwanese Department of Health (DOH) have implemented regulations requiring manufacturers to follow Good Manufacturing Practice (GMP) guidelines similar to those for pharmaceutical products. In addition, there have been efforts to control unsubstantiated medical claims about herbal products.

TCM in the US

According to the National Center for Complementary and Alternative Medicine at the National Institutes of Health (NIH),[2] TCM is widely used in the US. Although the

exact number is unknown, in 1997 it was estimated that some 10,000 TCM practitioners serve more than one million patients each year. According to the 2007 National Health Interview Survey, an estimated 3.1 million US adults had used acupuncture in the previous year. In addition, according to this same survey, approximately 17% of adults use natural products, including herbs, making them the most commonly used therapy. In another survey, more than one-third of the patients at six large acupuncture clinics said they also received Chinese herbal treatments there.

Several TCM products are available in the US, albeit as dietary supplements, nutraceuticals and cosmetics. These products are primarily available at Chinese ethnic stores, from private TCM practitioners or at health spas. Most are manufactured in China and imported. They are primarily used by people of Chinese origin living in the US, but there is some use by the general population as well. Some products such as ginseng have a much wider exposure due to use in several soft drinks and food products.

Some Chinese herbal treatments may be safe, but others may not. There have been reports of products contaminated with drugs, toxins or heavy metals, or not containing the listed ingredients. Some herbs are very powerful, can interact with drugs and may have serious side effects. For example, the Chinese herb ephedra (*ma huang*) has been linked to serious health complications, including heart attack and stroke. In 2004, FDA banned the sale of ephedra-containing dietary supplements used for weight loss and performance enhancement, but the ban does not apply to TCM remedies or herbal teas. No TCM product is currently approved by FDA as a medicinal product; therefore, these products cannot legally make any therapeutic or diagnostic claims. The main reasons are that these drugs lack clinical evidence of safety and efficacy established through appropriately designed clinical trials; their mechanisms of action are unclear; and their manufacturing information does not meet current GMP standards.

Clinical Trials with TCM Products

Clinical trials are an essential tool to demonstrate a drug product's safety and efficacy. Even though a product may have a long market history, prior human experience with the marketed drugs may be documented in many different forms and come from diverse sources, which may or may not meet modern quality standards. There are important reasons for demonstrating safety and efficacy. For example, once approved by FDA, a TCM drug product could be prescribed by any physician, with or without knowledge of TCM practices. Also, botanical drug components could lead to dangerous drug-drug interactions. Appropriately designed clinical trials provide essential evidence to support safety and efficacy, reveal drug interactions and potential side effects, and determine the appropriate treatment regimen for a product.

Acknowledging the unique characteristics of botanical drugs, FDA released *Guidance for Industry: Botanical Drug Products*[3,4] in June 2004, highlighting the key requirements and exceptions for developing such products. This guidance allows significant relaxations in data submissions compared to conventional drugs, for initiating human trials with botanicals under an Investigational New Drug (IND) application.

Since the guidance was released, several clinical trials have been initiated for TCM products. As of June 2009, about 450 clinical trials have been registered in the US (www.clinicaltrials.gov), with about 185 studies actively enrolling new patients. Most of these trials are being conducted in China, with about 70 in the US and the rest in other locations. Most are interventional studies evaluating the safety and efficacy of different TCM drugs for diverse indications.

Most of these clinical trials are being conducted under IND applications submitted to FDA. About 75% of the 450 clinical trials registered are Phase 2 and 3 trials, while the rest are Phase 1. Approximately 70 studies are in pediatric population and the rest in adults. About 25% of the studies follow a placebo-controlled, double-blind, randomized design. About 160 (35%) of the studies are sponsored by commercial concerns and the rest by academic, government and nonprofit organizations.

Filing an IND Application to Initiate TCM Drug Clinical Trials

FDA accepts data from clinical trials all over the world, whether conducted under an IND application or not. However, it is easier for manufacturers to demonstrate applicability of their data from other countries to the US population by conducting confirmatory or bridging clinical trials in the US. Before these studies can be initiated, an IND application must be filed with FDA. Even for trials conducted in other countries, if the intent is to use those data in support of an NDA in the US, it is highly recommended to file an IND to make FDA reviewers aware of the clinical development plan early so they can provide valuable feedback and suggestions.

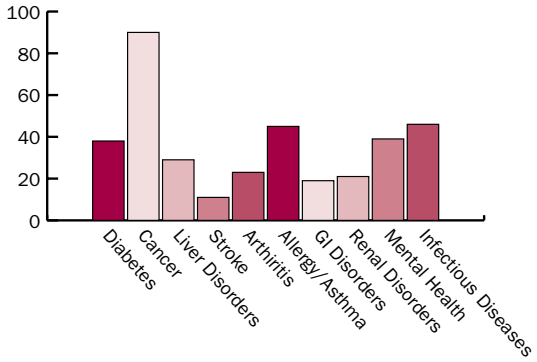
IND applications for TCM and other botanical products are very similar in format and content to INDs for conventional drugs; however, some specific issues need to be addressed carefully.

CMC Information

The most critical element of the IND application for botanical products is the chemistry, manufacturing and controls (CMC) information. A manufacturer must ensure the botanical drug's identity, purity, quality, strength, potency and consistency. Since the chief raw materials are plants, strict quality control measures for each plant raw material need to be implemented. They include genus/species identification by genotypic, phenotypic and chemical tests; growth conditions; processing methods; shipping and storage; and characterization of adulteration from other plant species. Traditional pharmacopoeial standards established in the country of origin are not sufficient for FDA, but the characterization has to meet FDA requirements as specified in the guidance documents. Special care must be taken if endangered species or habitats are employed, or if the raw material is collected from wild rather than cultivated plants. The manufacturer needs to demonstrate that plants are identified by trained personnel and, if possible, provide appropriate certificates of authenticity and analysis.

Apart from raw material control and characterization, the manufacturer needs to establish appropriate analysis, quality control and quality assurance measures such

Figure 1. Clinical Trials with TCM



(Source: www.clinicaltrials.gov, June 2009)

as standard operating procedures, general method of manufacture, and qualitative and quantitative description (composition) of the finished product. Manufacturing must be done under CGMP conditions. FDA acknowledges that botanical products are complex mixtures, that not all chemical components may be well defined and that the active components might not be identified. However, it does expect to see evidence that the manufacturer expended its best efforts to characterize the product by using a combination of tests such as spectroscopic and/or chromatographic fingerprints, chemical assay of characteristic markers and biological assays. Also, the agency expects the manufacturer to employ strict quality control of botanical raw materials and adequate in-process controls. A major concern with botanical drug products is heavy metals and minerals such as mercury and lead in the finished product. Content of these elements must be evaluated and justified, if present.

Toxicology and Pharmacology Data

Nonclinical pharmacology and toxicology information requirements for botanical drug products are far less stringent than those for synthetic or highly purified new drugs. A sponsor is required to list the general toxicity of the known components, the target organs and systems of toxicity, the relationship to dosage and duration of treatment to toxicity, and the pharmacological activity. In most cases, the long history of human exposure can be used to justify a waiver from FDA for conducting additional toxicology for initial clinical trials. However, if the product being pursued in an IND is new or different from the one with extensive human experience, nonclinical studies are needed before initiating human studies. Nonetheless, the number of nonclinical studies required could be far less than for a new chemical entity due to the nature of the product and its components. Based upon safety incidents identified in the initial clinical trials, additional nonclinical toxicity studies might be needed.

Previous Human Experience Information

To demonstrate safety in humans, a sponsor may present extensive previous human exposure to the traditional product using marketing data from all locations (domestic and international). Marketing information should include common dose and duration of treatment, approval status in other countries, number of doses sold, approximate number of people exposed to the drug, postmarketing safety information collected, if any, and status of large-scale manufacturing, storage and shipping capabilities. A major hurdle for TCM products is that since most were sold in China and Taiwan, a sponsor will need to translate all the supporting documents from Chinese to English for FDA. Efforts must be made to create a persuasive case with traditional data and modern marketing data of the sponsor's own and competitor products, either identical or similar in form, preferably for the same indication and route of administration. Exhaustive marketing data demonstrating extensive human exposure without any safety concerns could also help in obtaining a waiver of initial clinical trials and moving directly to pivotal trials in support of the NDA.

Importance of FDA Pre-IND Meeting

It is strongly recommended that sponsors compile all available information and discuss it, along with the design of the proposed preclinical and clinical trials, with the appropriate division of FDA in a pre-IND meeting. By discussing the development program with FDA prior to implementation, the sponsor receives critical feedback on the proposed studies and the acceptability of information. For such meetings, the sponsor should always request that representatives of the Botanical Review Team attend the meeting. All aspects of the product development plan should be discussed.

Conclusions

Botanical drugs hold great promise but also pose unique challenges in developing a product acceptable to FDA. Manufacturers need training and guidance in developing therapeutic products acceptable to Western regulators. The highest barrier for developers is to establish new evidence based upon clinical trials. Due to the high perception of efficacy in native populations, there is a strong placebo effect, leading to the failure of many products to meet the significant efficacy endpoint in a placebo-controlled study. Other challenges are lot-to-lot consistency in the finished product due to variations in the raw material, lack of good quality manufacturing, and lack of validated human exposure data. Most quality issues can be addressed by applying CGMP standards, and the evidence in support of efficacy and safety can be collected via appropriately designed clinical trials. TCM drugs have a greater chance of success than other herbal treatments due to a longer history of use in the US. There are many good product leads in TCM, several of which could end up being approved therapeutic products in the near future based upon sound scientific evidence.

References

1. Taylor L. "Plant Based Drugs and Medicines." Accessible at www.rain-tree.com/plantdrugs.htm.
2. Traditional Chinese Medicine: An Introduction. Accessible at http://nccam.nih.gov/health/whatiscam/chinesemed.htm#.
3. *Guidance for Industry: Botanical Drug Products* (June 2004). Accessible at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf.
4. Frequently Asked Questions on Botanical Drug Product Development. Accessible at www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090989.htm.

Authors:

Mukesh Kumar, PhD, RAC, is a senior director, regulatory affairs, at Amarex Clinical Research LLC, located in Germantown, MD, a full-service CRO offering strategic planning, trial management, data management and statistical analysis services for global clinical trials. Kumar is a member of the RAPS Board of Editors for *Regulatory Focus* and can be reached at mukeshk@amarexcro.com. **Hemant Jethwani, MS,** is a regulatory affairs associate at Amarex Clinical Research LLC. He can be reached at hemantj@amarexcro.com.