From Chinese Herbal Medicine to Botanical Drug: Regulatory Requirements from Taiwan to a United States IND Submission

There are many reasons why herbal medicines to treat diseases have not been widely accepted in the West. Recently, the regulatory environment in Taiwan has moved closer to Western standards in the approval of herbal medicines for new indications based on modern medicine. Also, the U.S. Food and Drug Administration (FDA) formally opened the regulatory door for the approval of botanical drugs. The regulatory requirements for herbal medicines in Taiwan and botanical drugs under an Investigational New Drug (IND) application in the United States are quite similar. A “pilot study” approach to “proof of the concept” of efficacy is encouraging in Taiwan. Experience obtained from two recent successful IND submissions to the FDA is very encouraging. One botanical contains a single herb and the other is a 15-herb combination. The major obstacle is the lack of documentation during the early product development phase and lack of animal studies. The manufacturer must demonstrate that it is trustworthy by producing verifiable data and documents during each step of drug development in a comprehensive and understandable manner so that regulatory agencies can understand what the manufacturer has done.

INTRODUCTION

Due to the economic downturn in Asia, many Asian countries are seeking strategic industries to stimulate economic growth. The botanical drug product industry is one potential area of high priority for many presumably “technologically-rich” countries or areas (1). Traditionally, botanically-derived drug products are obtained by isolation of the highly purified active component. This is no longer required for “botanical drug” products. The FDA formally opened the regulatory door by publishing a draft guidance on botanical drug products in August 2000 (2). At the same time, concerns about the decreasing number of innovative new drug submissions and approvals have affected the number of products launched. This creates an unprecedented interest in indigenous plant-based medicinal products, which have a long history of empirical use as a source of new research materials.

Both Oriental (including Chinese herbal medicine) and Western medicine have contributed greatly to their respective healthcare systems and the treatment of diseases. However, the two approaches differ significantly in concept, theory, and practice, especially in the design and use of drug products. Chinese medicine has a long history of use in Taiwan. Its medicinal products, however, were mainly based on empirical evidence and were manufactured according to traditional methods of processing. Recently, the regulatory environment in Taiwan has moved closer to the Western standards in the approval of herbal medicines as drugs.

This article compares the regulatory differences between Taiwan and the United States. We concentrate on the regulations for approving Chinese herbal medicines as drugs in Taiwan and as botanical drugs in the United States.

The use of herbal medicine for the treatment of diseases is well established in the East, but it has not been well accepted in the West. There are many reasons for this lack of acceptance:

- In Chinese herbal medicine, multiple herbs are commonly used, whereas Western medicine predominately uses a single plant. In Chinese herbal medicine theory, the use of multiple herbs is perceived as advantageous over a single herb. Appropriate herbs are combined to synergize the beneficial therapeutic effects and balance the adverse side effects. However, the use of multiple herbs also
leads to the horrendous quality control problems in Chinese herbal medicine,

- Chinese herbal medicine uses animal parts and heavy metals as part of some medications,
- Finished Chinese herbal medicine formulations and their appearance are not yet acceptable to the Western world. This problem has been alleviated somewhat by using modern technology to make so-called "scientific" or Western-like simple formulations such as capsules and tablets,
- Chinese herbal medicine manufacturers in the East are usually family-owned businesses. To gain global acceptance, Chinese herbal medicine manufacturers must learn the rules of international business and provide the world with evidence-based, science-based, clinically-driven, and verifiable data, and
- To compete with the giants, Chinese herbal medicine manufacturers must know how to protect their technology through patents and how to comply with international laws. During the drug development process, they must possess expertise in business management, and knowledge of regulatory and legal requirements and licensing in and out.

Despite some progress in the last several years, Taiwanese Chinese herbal medicine manufacturers are still far behind in this regard.

THE REGULATORY ENVIRONMENT WITH CHINESE HERBAL MEDICINE AS DRUGS IN TAIWAN

In Taiwan, the approval process for Chinese herbal medicine is separate from that for chemical and biological drugs. If a manufacturer of a Chinese herbal medicine claims an indication based on the theory of traditional Chinese medicine as defined in five classics of Eastern literature, only the Good Manufacturing Practice (GMP) requirement must be met. The requirement for efficacy and safety data is waived based on long-term human experience with the Chinese herbal medicine. However, if a manufacturer of a Chinese herbal medicine would like to claim an indication based on the theory of modern medicine, then approval requirements are stringent and mirror those of the West. This is an evolving trend and challenge for regulatory agencies.

The approval process for a Chinese herbal medicine as a new drug is divided into two stages: the so-called IND stage and the New Drug Application (NDA) stage. The Committee on Chinese Medicine and Pharmacy regulates the approval of Chinese herbal medicines. The Committee on Chinese Medicine and Pharmacy is responsible for promulgating, revising, and issuing regulations. It is also responsible for the approval, registration, and importation of the Chinese herbal medicines, including determination of the years of exclusivity, and approval of the design and protocol of the clinical trials.

The Center for Drug Evaluation assists the Committee on Chinese Medicine and Pharmacy in conducting primary and technical reviews for both INDs and NDAs. The Center for Drug Evaluation also assists the Committee on Chinese Medicine and Pharmacy in drafting related guidance. The combination of these two organizations is equivalent to the regulation of botanical drug products by the FDA.

Manufacturing, testing, and clinical trials must comply with international standards. Manufacturing of a Chinese herbal medicine as a new drug must comply with GMP. The analytical and animal testing, such as nonclinical pharmacological and toxicological studies, must comply with Good Laboratory Practice (GLP). Clinical trials must comply with Good Clinical Practice (GCP). The requirements for the manufacturing process and technique, and the control of raw materials, drug substance, and final drug product, are stringent.

There are a few small but active contract research organizations (CROs) in Taiwan. The involvement of these CROs will, in the long run, play an important role in assisting manufacturers of Chinese herbal medicines in placing their products on the international market.

THE REGULATORY ENVIRONMENT FOR BOTANICAL DRUGS IN THE UNITED STATES

In the United States, herbal medicines are frequently found in Oriental grocery stores and occasionally in health food stores. However, their importation status is highly questionable. Depending on the labeled claim, Chinese herbal
medicines could be approved as a food additive, a dietary supplement, a nonprescription medication (over-the-counter), or a prescription drug. The most common way to market Chinese herbal medicines is via the 1994 Dietary Supplement Health and Education Act, which provided a legal status for dietary supplements. However, the market for dietary supplements is highly competitive. Slick marketing and distribution/retail channels are the keys to success. However, disease claims are prohibited for dietary supplements. The market share of Chinese herbal medicines in the dietary supplements market ranges from nonsignificant to nonexistence.

In regard to submitting a Chinese herbal medicine as a botanical drug, the FDA does not distinguish between botanical or chemical drugs in its approval process. Any substance that claims to diagnose, prevent, treat, or mitigate disease is defined as a drug. The relaxation of United States regulatory requirements is primarily in the IND submission to allow an “unproven” botanical drug to proceed to rigorous human testing as soon as possible. The FDA is considered one of the most respected and stringent regulatory agencies in the world. The FDA is not prejudiced against Chinese herbal medicines. The approval of drug products derived from plants, complex mixtures, or unknown active components is not new to the FDA. Even before the FDA published the botanical drug guidance in August 2000, the FDA had accepted IND submissions for botanical drugs with unknown active components.

Based on a 2000 article about preclinical issues and the status of botanical drug products in the United States (3), as of 1998, at least 50 botanical drugs were submitted in original INDs and 14 were in the pre-IND stage. The article did not disclose the country of origin for these IND submissions. However, it is safe to say that Taiwanese manufacturers did not submit any submissions up to that time. We can state this because at that time, Taiwan did not have appropriate drug development expertise or marketing potential for those products even if they were approved; also, Taiwan lacked the vision, desire, and courage to meet the challenge.

A COMPARISON OF BOTANICAL DRUG IND REQUIREMENTS IN TAIWAN AND THE UNITED STATES

The IND requirements in Taiwan are largely similar to those in the United States. However, because Chinese herbal medicines have a longer history of use in Taiwan, there is a better understanding of the safe nature of these drugs and greater confidence among the public. As a result, the authority is prepared to adopt a more flexible attitude toward safety issues for IND applications for Chinese herbal medicines. Taiwan’s requirements are:

- For botanical products with little human experience or unknown safety, a full IND is required to start a phase 1 study,
- For botanical products that are already on the market but where optimal use for the new indication might be beyond previous human experience, reduced chemistry/manufacturing/controls and full pharmacology/toxicology data are required to start a phase 1 study, and
- For botanical products that are already on the market where safety in the proposed therapeutic dose is not a concern, reduced chemistry/manufacturing/controls data are required.

These requirements encourage a “pilot study” approach to “prove the concept” of efficacy first with the traditional regimen before beginning a serious drug development process starting with a phase 2 study.

PROBLEMS WITH APPROVAL OF CHINESE HERBAL MEDICINES IN THE UNITED STATES AND SOLUTIONS

Due to the economic downturn in Asia, many Asian countries are desperately looking for an alternative to stimulate economic growth. The biotechnology and pharmaceutical areas are high on their wish list. The Western world also realizes that the number of approved new drugs has gradually decreased in each decade and yet, the discovery of new drugs with botanical origin remains untouched. In 2002, the approval of innovative and significant new drugs in the United States fell sharply (4). Botanical drugs from the East can be a welcome alternative.
It is quite puzzling that Chinese herbal medicine manufacturers have not been pursuing this opportunity. The United States is the largest pharmaceutical market in the world and Chinese herbal medicines cannot even occupy a small fraction of that market. It is even more puzzling that Taiwanese manufacturers of Chinese herbal medicines are not seeking approval of their products in the United States, since the approval requirements are the same in both countries. Other than those reasons mentioned earlier, the author has also observed:

- Taiwanese manufacturers of herbal medicine are in transition from old-fashioned development and sales to becoming knowledge-based companies. It will take time for visionary leaders to emerge from the transition,
- The Asian market by itself is huge and in transition. There is plenty of money to be made at this time and there is no need to pursue opportunities outside of the comfortable environment of Asia. Alternatively, there is a lack of desire or courage to explore opportunities outside of Asia,
- The modern global pharmaceutical business has drastically changed many times over the last decade. Large pharmaceutical companies are using mergers and acquisitions to grow and to capture the lion’s share of the market. Small pharmaceutical companies are getting faster and smarter, and serving as providers of innovative value-added technology to the pharmaceutical giants. Traditional herbal medicine manufacturers have a hard time adjusting to the current pharmaceutical business environment,
- Even though the regulatory requirements appear to be the same, the interpretation of the requirements and the spirit are not the same. Asian companies consider GMP, GLP, and GCP regulations hurdles while United States companies accept them as a way of doing business. Because of the different interpretations and emphasis, Asian companies that easily comply with Asian requirements may still have problems complying with United States requirements, and vice versa, and
- The quality of Chinese herbal medicines is questionable by Western standards. Without quality, there will be no trust and no world-class pharmaceutical company. Some Taiwanese manufacturers produce high-quality products, or at least have the desire to achieve high quality, but their lack of knowledge of the required documentation hampers their ability to communicate to the world. Today, the single most acute problem for Taiwanese (or Asian) manufacturers is the documentation system. Manufacturers must produce verifiable data and document each step of their drug development in an understandable manner so that regulatory agencies worldwide can understand what the manufacturers have done.

EXPERIENCE WITH TWO RECENT BOTANICAL DRUG SUBMISSIONS IN TAIWAN

As of July 2003, to the best knowledge of the authors, nine successful INDs have been submitted as Chinese herbal medicine drugs in Taiwan and two successful INDs have been submitted as botanical drugs in the United States. The two United States IND submissions were for a single herb product and a 15-herb product. It is important to note that the studies were conducted in the country of origin, which also provided the supportive documentation. For the single herb product, all documentation, including chemistry/manufacturing/controls data, preclinical studies, and data on prior human experience, were obtained in Taiwan. For the 15-herb product, documentation and studies were obtained in China.

One common attribute of the success of both submissions is that the compilation of documentation met the United States standard. In addition, both products had prior market experience, were protected by patents, and demonstrated good quality control with well-established manufacturing processes and specifications. The manufacturers provided reduced toxicology studies for both products.

These successful IND submissions support the FDA’s commitment to allowing botanical drugs with no safety concerns to proceed to the clinical study phase with reduced documentation. The challenge for Taiwanese sponsors is to determine how to compile the information and documentation to convey the message to the FDA that they are serious and responsible pharmaceutical players, in an understandable manner.
CONCLUSION AND REASONS FOR OPTIMISM

With recent changes in the regulations, the FDA has essentially opened the door for the approval of dietary supplements and botanical drugs. Even in the most stringent areas of drug approval, there are reasons for optimism. All of the following are possible: source control of botanical raw materials through Good Agricultural Practice; quality control with modern analytical technology; clinical proof through proper design; patent protection and market exclusivity; business ventures such as initial public offerings after receiving United States or Asian market approval; codevelopment and comarketing with large pharmaceutical companies after the “proof-of-concept”; and FDA approval. After FDA approval, worldwide acceptance is also possible.

Currently, Taiwan lacks the business know-how and documentation system to interact with the world. By working with the seasoned business managers and Western-trained scientists, we can quickly fill these gaps. The two recently approved Taiwanese IND submissions to the FDA demonstrate that regulatory approval is possible. It is up to the Chinese herbal medicine manufacturers to demonstrate that they can provide real evidence and prove to the world that they can cure incurable diseases, can produce products of the highest quality consistently, and have the business know-how to make that happen.

REFERENCES
