Developing Botanical Products from India for the US Market

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Botanical or herbal medicine is an age-old practice. Nonetheless, with only 10% of the Earth's estimated 250,000 species of plants considered medicinal, botanicals are the "sleeping giant" of drug development. Indeed, increased side effects of chemical drugs, lack of treatment for several chronic diseases, high cost of new drugs, microbial resistance and emerging diseases are sparking renewed public interest in complementary and alternative medicines.[1] The terms "complementary medicine" or "alternative medicine," which are used interchangeably with "traditional medicine" in some countries, refer to a broad set of healthcare practices that are part of a country's tradition and are not integrated into the modern healthcare system.

For example, medicinal plants play an important role in Indian culture and are widely used for both general health and specific therapeutic applications. Ayurveda is an ancient system of traditional medicine widely practiced in India. The word "Ayurveda" means science of life (Ayu = life + Veda = knowledge/science). Traditional medicine is one of the three components of medical practice in India.

Indian Systems of Medicine

The three types of Indian medical practice are regulated and managed by different and distinct systems. Modern medicine is regulated primarily by the Indian Council of Medical Research (ICMR). There are about 650,000 physicians practicing in India[2] who use modern drugs, biologics, medical devices and similar medical products. This practice is indistinguishable from that in the US and other Western countries.

Traditional medicine, on the other hand, involves nonconventional therapeutic and diagnostic techniques described in ancient literature. Traditional medicine systems primarily include Ayurveda, Unani, Siddha and homeopathy, although there are several variants. Traditional therapy involves diagnosis and treatment for general health and specific treatment of diseases but uses few defined preventative products such as vaccines. Multicomponent drug formulations, custom drug formulations and device-drug combination products are used. Traditional medicine is regulated by the Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy (AYUSH) under the Ministry of Health and Family Welfare of the government of India. There are about 750,000 registered practitioners of this medicine in India.[3]

A third distinct practice comprises alternative treatment methods such as yoga, naturopathy and acupressure. These techniques rarely involve conventional drugs or traditional medicines, focusing instead on lifestyle techniques and products. Alternative therapy also is regulated by the department of AYUSH; however, regulation is very limited. This practice does not require formal registration and hence the actual number of practitioners is unknown, but by some estimates there could be as many as a million alternative medicine healers.

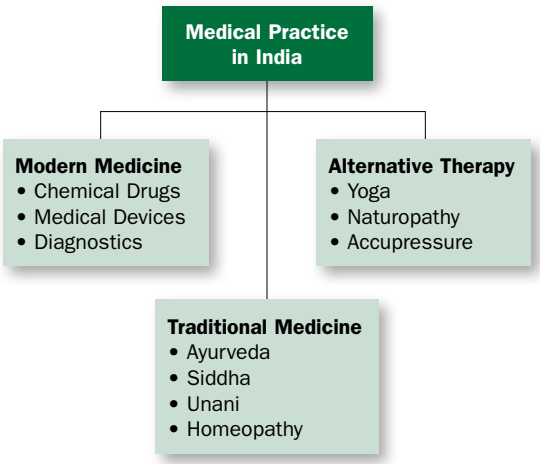
Ayurveda

According to the Indian Council of Scientific and Industrial Research (CSIR), Ayurveda is one of the best-documented traditional systems, with a sound philosophical, experiential and experimental basis. Ayurvedic medicine dominates traditional medicine in India with its 85% share of the market, although about 61% of the traditional medicine practitioners are Ayurvedic doctors and 30% homeopathy doctors.

Ayurveda is one of the oldest systems of traditional medicine in the world, with a documented history of practice dating back 3,000–5,000 years. This system of medicine is based upon ancient, sacred texts such as the *Vedas, Charak Samhita* (at 1,200 years old, the most ancient treatise on healthcare and medicine) and *Sushrut Samhita* (on surgery). Ayurvedic medicine is taught at Ayurvedic medical schools and involves study, memorization and training in practical application of these ancient texts.[4]

The philosophy of Ayurveda goes beyond treating and curing disease to maintaining and improving health. Based upon this philosophy, an individual is assessed for complete health status and provided treatment customized to his or her requirements as judged by the physician. In many ways, Ayurvedic medicine is comparable to the field of personalized medicine. Treatment is based upon a well-developed

Figure 1. Medical Practice in India



system using several botanical formulations. Though Ayurveda is practiced for both acute and chronic illnesses, the popular belief is that it is more suitable for the latter. Hence, patients consulting Ayurvedic doctors most commonly seek treatment for arthritis, skin diseases, gastrointestinal disorders, endocrinal diseases, etc. At present there are more than 5,000 Ayurvedic hospitals in India, about half of which are run by the government. Both inpatient and outpatient facilities are available.

Ayurvedic literature describes the use of herbs, animal parts and minerals; however, the vast majority, or 94%, of Ayurvedic medicine is plant based, with more than 2,660 herbs listed. Therefore, pure herbal and herb-mineral combinations are the most common products used in Ayurveda. These products are available as pills, powders, wines, oils and creams or ointments. Some of the formulations use heavy metals such as mercury or lead. Unlike the Western medical community that believes heavy metals to be unsafe,[5] Ayurveda recommends heavy metal ashes for use in treatment of various chronic disorders. There have been a few clinical studies, primarily to evaluate safety issues with the use of heavy metals and minerals, but the results have been inconclusive. AYUSH has developed monographs on several Ayurvedic herbs and traditional formulations under various initiatives such as the *Indian Herbal Pharmacopoeia*, *Ayurvedic Pharmacopoeia* and the *Ayurvedic Formulary* of India. In addition, several companies have built private chemical and germplasm libraries based upon traditional Indian plants that can be used in drug leads.

Practice of Indian Traditional Medicine in the US

Herbal products have been available in the US since the European settlement of the country, and probably earlier due to use by Native Americans. Most herbal products currently on the market are concentrated extracts, fluid extracts and tinctures.[6] There have been a few clinical trials of these products, but few studies have been able to establish clinical efficacy.[7,8] Together with poorly defined chemistry and manufacturing issues, the lack of clinical trials has limited the herbal products approved by the US Food and Drug Administration (FDA), and these few are mostly dietary supplements.

Currently, there are no New Drug Applications (NDAs) based on Ayurvedic products under review by FDA. All herbal remedies based on Ayurveda are sold as dietary supplements and are not allowed to make medicinal or preventative claims on their labels. There are several alternative medicine clinics that offer Ayurvedic therapies for the treatment of chronic conditions such as rheumatoid arthritis, asthma, constipation, anxiety, chronic fatigue syndrome and allergies.[9] Also, Ayurvedic formulations are used at a few health spas and health resorts, where general health claims are made and these products are promoted as a way to relax as well as to smooth and rejuvenate the skin.[10] According to a National Health Statistics Report (NHSR) published in 2007, nearly four in 10 people in the US report using an herb for treatment of health conditions and/or health promotion.[11] Further, according to the *Nutrition Business Journal*, the market for herbal supplements has steadily expanded over the past 10 years.

Developing Ayurvedic Medicinal Products for FDA Approval

Unlike conventional drug products, traditional products have the advantage of safety established via long human exposure, well-established manufacturing processes and general acceptance by consumers. The manufacturer of a traditional medicine product needs to establish evidence of safety and efficacy via appropriately designed clinical trials, characterize the chemical nature of the formulation and implement current Good Manufacturing Practice (CGMP) to provide support for a marketing approval application (NDA). Hence, these products

could conceivably be approved by FDA in less time, with fewer clinical and preclinical studies and lower costs than conventional drugs. The key to success is using the available information strategically, identifying the gaps in the information and creating plans to fill those gaps.

It has been proposed that Ayurvedic products follow a development pathway very different from that of conventional drugs. A typical drug development pathway involves identification of the target indication and the potential chemical or biological agent (the lead molecule) to counter that target; development of the lead molecule; and finally, testing in preclinical and clinical trials to demonstrate safety and efficacy in human usage. In contrast, it is believed that Indian traditional drug products, and by extension all similar products from India and other locations, should be developed via a reverse process. Ayurvedic products currently on the market in India or other countries should follow this process: characterization in terms of chemical components and content of each component in the final formulation, manufacturing step optimization, characterization of raw materials used and physical characteristics, such as dissolution, melting temperature, stability, storage conditions, etc., to the greatest extent possible. Per the botanical product guidance released by FDA, it is acceptable for a botanical product to have multiple components and for the chemistry, manufacturing and controls (CMC) information to be less than perfect. A sponsor needs to demonstrate the best possible effort to characterize a given product to identify any potentially toxic ingredients and all active ingredients.

Once the appropriate CMC information is collected, the sponsor should plan clinical trials to demonstrate the formulation's safety and efficacy for the target indication. Since these products have a long history of human exposure with no known safety concerns, it is possible to obtain a waiver from FDA regarding Phase 1 clinical studies solely to demonstrate the product's safety. Since pharmacokinetic (PK) information is usually not available for these products, it is also useful to collect PK data from the clinical trials. In addition, a sponsor should plan to conduct basic research to understand the mechanism of action of the product. However, since traditional products are composed of multiple components and could have trace elements of importance, it might not be possible to demonstrate the exact mechanism of action. Provided a product is safe and efficacious, an NDA can still be filed successfully.

Compared to conventional drugs, botanical prescription products based upon traditional Indian drugs can be developed successfully in far less time and with far less expense. A sponsor needs a reliable product development and regulatory strategy. Discussing the regulatory strategy and the clinical development plan with FDA early in the process could be very helpful and indeed critical to the NDA's success. FDA has established the Botanical Review Team (BRT) within the Center for Drug Evaluation and Research (CDER) to assist developers of such products in obtaining agency feedback on their products. BRT is composed of experts in medicinal plant biology, pharmacology of herbal preparations and clinical uses of botanical products.

Practical Issues in Developing Botanical Products

Traditional products from India do offer some unique challenges in addition to those of typical botanical products. These range from scientific and regulatory issues to financial and legal matters.

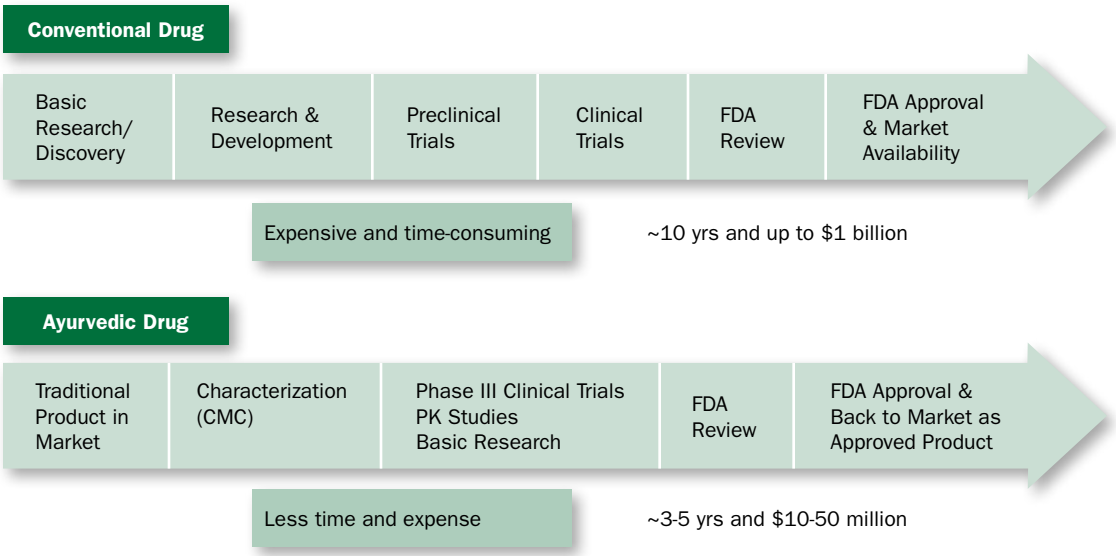
Demonstrating Scale of Human Use

A key claim to the safety of Ayurvedic and other traditional drug products is their use by a large segment of the population for a very long time without any safety concerns. For FDA to accept that claim, a manufacturer needs marketing and sales data to show the number of doses sold, number of people for whom the drug has been prescribed, duration of market availability, populations exposed to the drug, etc. In India, this kind of information has not been collected and, even for well-established manufacturers, is hard to compile. Such information can be compiled for the last decade or so at the most.

Product Safety

As mentioned above, several Ayurvedic drugs contain heavy metals such as mercury and lead, which are considered unacceptable in the US. Ayruvedic treatment involves a systematic process whereby a trained Ayurvedic doctor uses products containing such components based upon a patient's individual requirements. However,

Figure 2. Developing Ayurvedic Medicines for FDA Approval



when Ayurvedic treatments are offered to a wider market and prescribed by physicians not familiar with the Ayruvedic practice, such components must either be removed from the formulation or justified scientifically. Traditional medicine also is challenged by sometimes misplaced trust in the product's safety. Many people believe that because medicines are herbal (natural) or traditional they are safe (or carry no risk of harm). However, traditional medicines and practices can cause harmful, adverse reactions if the product or therapy is of poor quality, or it is taken inappropriately or in conjunction with other medicines. Increased patient awareness about safe usage, as well as more training, collaboration and communication among providers of traditional and other medicines, are important.

Quality Issues

It can be difficult to assess the quality of finished herbal products because it depends upon the quality of the source materials (which can include hundreds of natural constituents) and how elements are handled in production processes. In addition, botanical or herbal products are affected by the growth conditions of the source plants such as weather, season, soil quality, use of fertilizers and irrigation conditions. Following CGMPs in the production of botanical products is hard but has been done successfully for many products. AYUSH requires manufacturers of Ayurvedic and other traditional drugs to follow CGMP conditions very similar to those for conventional drugs. Key manufacturing issues are controlling variation in product lots, avoiding contamination with environmental agents such as pollutants and insects, ensuring quality control of raw material and process material, and instituting quality assurance processes.

Sustainability

Herbal materials for products are collected from wild plant populations and cultivated medicinal plants. The expanding herbal product market could lead to over-harvesting of wild plants and threaten biodiversity. Poorly managed collection and cultivation practices could lead to the extinction of endangered plant species and the destruction of natural resources. Efforts to preserve plant populations and knowledge on how to use them for medicinal purposes are needed to sustain traditional medicine.

Counterfeit Products

A plethora of junk products are available in the market. Any botanical product in the market has to deal with several counterfeit products claiming similar ingredients. Due to long market exposure, popular products are routinely counterfeited and sold as dietary supplements.

Intellectual Property Concerns

The biggest concern for a botanical product developer is protecting its intellectual property. Since these products are based upon historical literature, have a very long history of use, and are manufactured and

sold by several vendors all claiming the same composition, it is very hard to enforce intellectual property rights (IPR). Most of these products are not eligible for traditional methods of IPR protection such as patents and might be impossible to protect by trade secrets due to the wide availability of knowledge about production methods. However, FDA does offer market exclusivity to the first product of a class. By being the first to develop a botanical product, a sponsor is guaranteed up to five years of marketing exclusivity during which time FDA will not approve any other product claiming similar composition and benefits. Also, since unapproved products cannot claim medical benefits, cannot be covered by insurance and have to be sold as dietary supplements with general health claims, the sponsor of the first NDA does have a reasonable advantage over the competition. That advantage, coupled with the fact that the investment in developing these products is far less compared to conventional drugs, makes it reasonable to expect a good return on investment.

Conclusions

The World Health Organization (WHO) has recognized the importance of botanical products and encourages its members to cooperate in promoting the use of traditional medicine for healthcare. It advises supporting traditional medicine and integrating it into national health systems together with implementing national policies and regulations to ensure safety and quality. Botanical product guidance documents on supporting policies and pathways have been released by FDA and the European Medicines Agency (EMEA) to encourage development. There is a concerted effort by regulators all over the world to establish reliable scientific evidence for safe, effective and high-quality botanical products. Botanical products hold the promise of safe and effective treatments for a variety of ailments. In addition, it is expected that traditional medicine will evolve to produce better-quality products with modern scientific evidence of efficacy.

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