Regulatory Issues for Traditional Medicine

Introduction

Traditional medicine is a broad term encompassing health practices, approaches, knowledge and beliefs which incorporate herbal, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being. There has been a lot of interest, in the traditional medicine for its potential contribution to health care. However, there are a lot of concerns about the traditional medicine in areas of efficacy, safety and quality. Unregulated or inappropriate use of traditional medicines and practices can have negative or dangerous effects.
Among the traditional approaches, herbal medicines present unique challenges in research and regulations.

Current regulatory issues for herbal medicines

There are several regulatory concerns in relation to research applications and commercialization of herbal medicines.

Standardization of herbal drugs

For safe and effective use of herbal drugs, consistency in composition and biologic activity are essential requirements. However, herbal drugs frequently fail to meet this standard, as there are problems such as
1) Difficulties in identification of plants,
2) Genetic variability,
3) Variations in growing conditions,
4) Diversity in harvesting procedures and processing of extracts, and
5) A lack of information about active pharmacologic principles.
The use of chromatographic techniques and marker compounds for the standardization of herbal products can ensure batch-to-batch consistency; however, this does not ensure consistent pharmacologic activity or stability.
With herbal medicines what is on the label and what is in the bottle may differ considerably. In a study of ginseng preparations, the amount of ginsenosides varied from 11.9-327.7% of the amount on the label. Medical letter cautions, "Their (herbal medicines) potency may vary and their purity is suspect," Australian medicines regulatory body the Therapeutic Goods Administration, suspended production license of Pan Pharmaceuticals after an audit, which revealed problems with company's quality control standards.

Quality of herbal preparations

If an herbal remedy is effective, quality assurance is needed to ensure that the product has the expected effects. Even in the absence of data on efficacy, quality assurance is important, as quality is a critical determinant of safety as well.
Adulteration of plants is serious problem. Some of the common adulterants are: botanicals, toxic metals, microorganisms, microbial toxins, pesticides, and

fumigation agents.
A US investigation reported that 32 percent of marketed Asian patent medicines contained undeclared pharmaceuticals or heavy metals. The drugs most frequently found were ephedrine, chlorpheniramine, methyltestosterone, and phenacetin; 10 to 15 percent contained lead, mercury, or arsenic. The incidence of heavy metal contamination is not known, but one study showed that 64% of samples collected in India contained significant amounts of lead (64% mercury, 41% arsenic and 9% cadmium). This can cause serious harm to patients taking such remedies and could confound the assessment of safety in a clinical trial.
Quality has to be assured at all stages – herbal raw materials, processing of herbals and finished herbal medicines

Evidence of Clinical Efficacy

Scientific evidence from randomized clinical trials is only strong for many uses of acupuncture, some herbal medicines and for some of the manual therapies. Only a small fraction of the thousands of medicinal plants used worldwide has been tested rigorously in randomized, controlled trials. Even if the animal studies or anecdotal clinical experiences are promising and use of an herb is widespread, such observations cannot predict the results of well designed randomized, controlled trials.

Evidence-based studies on the efficacy and safety of traditional medicines are limited. The data available is mostly experimental or in animals. Most trials do not report hard efficacy endpoints and duration of observation periods is generally short. The clinical relevance of the observed effects is not always clear. For instance, most Indian trials of hepatoprotectice agents are open and uncontrolled. As most acute liver conditions have a natural recovery, it is difficult to link the improvement to the herbal product.
The essential ingredient in most formulations is not precisely defined. High quality studies are necessary to evaluate and compare the value of traditional drugs to modern medicine.
A fundamental problem in all clinical research of herbal medicines is whether different products, extracts, or even different lots of the same extract are comparable and equivalent. For example, Echinacea products can contain other plant extracts; use different plant species (E. purpurea, pallida or angustifolia), different parts (herb, root, both), and might have been produced in quite different manners (hydro- or lipophilic extraction). Even different species may be known by the same name in local language. Brahmi refers to *Centella asiatica* and *Bacopa monniera*.

The herbal industry is not required to conduct clinical trials, and the industry professionals argue that it would be not be possible to recover the high research costs, as herbal products can not be patented as easily as new chemical entities. Nevertheless, randomized, controlled trials are the best way to demonstrate the efficacy of any medicine, herbal or conventional.

Safety Concerns - Adverse Reactions and Drug Interactions

Herbal medicines are generally considered comparably safer than synthetic drugs. While this may be probably correct, case reports show that severe side effects and relevant interactions with other drugs can occur.

For instance, the herb Ephedra marketed as a dietary aid in USA, led to at least a dozen deaths, heart attacks and strokes. Other well-known safety issues have been hepatotoxicity of kava and renal effects of aristolochic acid. Besides, drug interactions of herbal drugs are of a serious concern. For example, hypericum extracts can decrease the concentration of a variety of other drugs by enzyme induction. Serious adverse effects have been reported when the addition of St. John's wort caused serum levels of cyclosporine and antiretroviral agents to fall to sub therapeutic levels. Garlic is reported to increase clotting time in patients taking warfarin.

Lack of regulatory standards regarding the efficacy and safety of herbal products did not arouse much concern in the past, as these products were often perceived as so safe that even if they were ineffective, little harm resulted. However, the situation is changing now and there is an increasing body of literature on the side effects and interactions of herbal medicines. Besides the direct risks of adverse effects and drug interactions there is an indirect risk that an herbal remedy without demonstrated efficacy may compromise, delay, or replace an effective form of conventional treatment.

WHO has urged the governments to establish regulatory mechanisms to control the safety and quality of products.

Global Regulatory Scene

The above issues have led to an increasing regulatory focus on herbal products in US and Europe. Some of the recommendations are:

- Plants and herbal remedies should prepared strictly in the same way as described in the literature while incorporating GMP norms for standardization
- For herbal remedies, it may not be necessary to undertake Phase 1 studies
- If there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months, toxicity studies (4-6 weeks toxicity study in 2 species of animals) are needed for phase 2 trials.
- For Phase 3 trial toxicity studies (4-6 weeks toxicity study in 2 species of animals) are needed.
- Clinical trials should be carried out with herbal preparations only after standardization and identification of markers to ensure that the substances being evaluated are always the same.
- Ethical guidelines (patient information, informed consent, protection of vulnerable populations etc) for biomedical research should be followed.

- Clinical trials should to be approved by the appropriate scientific and ethical committees of the concerned Institutes.
- Clinical trials should be carried out only when a competent traditional medicine physician is a co-investigator