Herbal Medicine: Regulation and Marketing

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Given the expansion of herbal medicine, the overall quality, safety and efficacy must be subjected to critical examination if the intention is to safeguard public health. There are quality concerns on the products already in the market. Adulteration of contents, ingredients differing from label and unsupported or misleading claims are reported in several studies. This article proposes three areas that can be standardized to ensure quality, safety and efficacy of herbal medicines. The first is ensuring good agriculture and harvesting practices for the plant raw materials. Second is good manufacturing practice of producing medicinal preparation (liquid or solid form) from the raw materials. Third, develop a standardized and acceptable clinical trial design to demonstrate safety and efficacy. The regulatory agencies of some developed countries have published guidelines to ensure the quality of herbal medicines. Example of these guidelines are the botanical drug product guidance of the US FDA, the evidence for quality of finished natural health products guidance of the Health Canada and the guideline on quality of herbal medicinal products by the EMA. They specify different registration pathways. Registration pathways in Europe are traditional herbal registration (THR) or conventional marketing authorization (CMA). In the USA, it can be registered as dietary supplement (DS) or botanical drug (BD). In the Philippines herbal medicines taken orally can be registered as herbal medicine (HM), traditional use herbal product (TUHP) and dietary supplement (DS). Requirements for registration in the three regions compared include quality control and good manufacturing practices, evidence of safety and toxicologic studies and evidence of efficacy or clinical trials, but it all depends on the product to be registered or the chosen pathway for registration. After approval for marketing, there must be a methodological approach for post-marketing safety based on sales data and information on adverse drug reactions of newly introduced herbal medicinal products in the market.

Keywords: Herbal medicine, safety, efficacy, quality

Introduction

Herbal medicines have become attractive and affordable alternative to synthetic drugs. They are standardized herbal preparations consisting of complex mixtures of one or more plants' seed, berries, roots, leaves, barks or flower for the treatment of various diseases. The WHO defines it as drugs with active ingredients from plant parts or plant materials in crude or processed state plus certain excipients, i.e., solvents, diluents or preservatives. Combinations with chemically defined active substances or isolated constituents are not considered to be herbal medicines. Usually, the active principles responsible for their pharmacological action are unknown. For this reason, they are not used for emergency treatment. However, they are used for wide therapeutic purpose and is getting great acceptance by the population. The WHO estimates that about 80 percent of world population presently use herbal medicine for primary care. This is because of poverty and lack of access to modern medicine in developing countries.[1] But it is not only in poor and developing countries where herbal medicine has become popular. In the UK, it is a popular form of treatment used by millions of people each year. They are commonly used by district nurses as a supplement to the treatment and care for their patients. As a result, interest in herbal drug development has increased.

Currently, it is estimated that about 25% of all modern medicines are directly or indirectly derived from plants.[2] This has increased the international market and trade of herbal medicine. A few years ago, only small companies had interest in this market. But because of the increasing cost of drug development

by finding new active compounds or combinations of compounds, major pharmaceutical companies have also demonstrated renewed interest in investigating plants as sources for new lead structures and for the development of standardized drugs with proven efficacy, safety and quality.[3]

Given the expansion of herbal medicine, the overall quality, safety and efficacy must be subjected to critical examination if the intention is to safeguard public health. There are quality concerns on the products already in the market. Adulteration of contents, ingredients differing from label and unsupported or misleading claims are reported in several studies. Lastly, some of these products have vague evidence for safety and efficacy. Thus, in the interest of protecting and providing the consumer with high-quality, safe and effective herbal medicines, a standardized regulatory approach that will ensure good manufacturing practices and scientific testing and review process prior to marketing is necessary.[4]

Areas for Regulation

Herbal medicines are marketed as standardized preparations in the form of liquid (syrup or suspension), solid (tablet, capsule or powdered extract). They are prepared by planting followed by harvesting of plant parts for production of medicinal preparation. Variation in this stage makes the availability of standardized and quality raw materials often problematic. Ethanol, water, or mixtures of ethanol and water are used in the production of fluid extracts. Solid or powered extracts are prepared by drying of the harvested material and grinding to powdered form or evaporation of the solvents after the process of ethanol or water extraction. Because the active ingredient is not frequently known, empirical use in folk medicine is often the evidence available instead of well-designed controlled trials. Compared with well-defined synthetic drugs, standardization of herbal medicines medicine production and monitoring its use are feasible but not easy. But this is necessary to ensure patient safety.[5] Based on a WHO global survey on the national policy and regulation of traditional medicine, there are three common difficulties and challenges i.e. information sharing, lack of safety monitoring of herbal medicines and lack of methods to evaluate safety and efficacy.

In this article, the authors are proposing three areas that can be standardized to ensure quality, safety and efficacy of herbal medicines. The first is ensuring good agriculture and harvesting practices for the plant raw materials. Second is good manufacturing practice of producing medicinal preparation (liquid or solid form) from the raw materials. Thirdly, develop a standardized and acceptable clinical trial design to demonstrate safety and efficacy.

Good Agricultural and Collecting Practice

Plant constituents vary and this affect the quality of plant medicinal component. The source and quality of raw materials play a pivotal role in guaranteeing the quality and stability of herbal preparations. Other factors such as the use of fresh plants, temperature, period and time of collection, method of collecting, drying, packing, storage and transportation of raw material, age and part of the plant collected, etc., can greatly affect the quality, safety and efficacy of herbal medicines. Thus, proper standardization and quality control of raw material and the herbal preparations themselves should be permanently carried out. The WHO Guideline for Good Agricultural and Collecting Practice for Medicinal Plants is a good standard to be applied.[6]

Good Manufacturing Practice

The procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional medicines. Conventional medicines are produced from synthetic materials by means of reproducible manufacturing techniques and procedures. Herbal medicines are prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources. Because of the inherent complexity of naturally grown medicinal plants and the variable nature of cultivated ones, the production and primary processing has a direct influence on the quality of herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality. The WHO Guidelines on good manufacturing practices for the manufacture of herbal medicines is a good standard to be applied.[7]

Evidence of Safety and Efficacy

Herbal medicines must be scientifically proven to be safe. The general idea that herbal drugs are very safe and free from side effects is based on anecdotal reports and not scientific evidence. Plants have hundreds of unknown constituents and some known constituents are toxic when used at inappropriate dose, a good example is digoxin from foxglove (Digitalis lanata). Like all drugs, herbal medicines have potential adverse reactions and interactions with other medicines. Thus, evaluation of the safety should include at least in vitro and in vivo studies.[8]

With regards to efficacy, a survey of the published literature showed that few well-controlled double-blind (placebo-controlled) trials have been carried out with herbal medicines. Several factors might have contributed to this. First there was lack of standardization on the quality control, inappropriate

dose, short duration of treatment and inappropriate placebo comparison or outcome observation may have resulted to non-significant results. In some trials, inappropriate small sample size may have resulted to lack of statistical significance. Non-significant studies have less chance of getting published. Well conducted controlled clinical trials must be done with adequate dose, duration of treatment and sample size.

Global Regulatory Practice

The regulatory agencies of some developed countries have published guidelines to ensure the quality of herbal medicines. Example of these guidelines are the botanical drug product guidance of the US FDA, the evidence for quality of finished natural health products guidance of Health Canada and the guideline on quality of herbal medicinal products by the EMA. Comparison of the registration pathways and requirements in the US, EU and Philippines is shown in Table 1. Registration pathways in Europe are traditional herbal registration (THR) or conventional marketing authorization (CMA). In the US, it can be registered as dietary supplement (DS) or botanical drug (BD). In the Philippines herbal medicines taken orally can be registered as herbal medicine (HM), traditional use herbal product (TUHP) and dietary supplement (DS). Requirements for registration in the three regions compared include quality control and good manufacturing practices, evidence of safety and toxicologic studies and evidence of efficacy or clinical trials, but it all depends on the product to be registered or the chosen pathway for registration. Registration for herbal medicine, botanical product or conventional marketing authorization are often complicated and the requirements are similar to registration of synthetic products. The alternative pathways such the TUHP, THR and DS are often simplified. In the US, dietary supplement does not even have to be registered with the FDA. While regulatory requirements differ from one country to another, the intention is to provide quality, safe and effective herbal products to the public. The standards define the quality of these products, also eliminate dangerous counterfeit, substandard, adulterated and contaminated products.[9]

Promotions and Marketing

Once approved the policies on herbal medicine does not specify specific guidelines on promotions and marketing.

Table 1. Comparison of regulatory pathways for herbal medicines[10]

	Philippines	United States	Europe
Registration Pathway	• Herbal Medicine (HM) • Traditionally Used Herbal Product (TUHP) • Dietary Supplement (DS)	• Botanical Drug (BD) • Dietary Supplement (DS)	• Conventional Marketing Authorization (CMA) • Traditional Herbal Registration (THR)
Evidence of Quality	• Quality Control tests and Good Manufacturing Practice for both HM, TUHP and DS	• None for DS • Quality Control tests and Good Manufacturing Practice for BD	• Quality Control tests and Good Manufacturing Practice for both THR and CMA
Evidence of Safety	• Toxicological test for HM • Evidence of safety based on bibliographic documents for traditional use	• Toxicologic tests for BD • None for DS	• Toxicological test for CMA • Bibliographic data for THR
Evidence of Efficacy	• Clinical trials for HM • Evidence of claimed application based on bibliographic documents for traditional use	• Clinical trials for BD • None for DS	• Clinical trials for CMA • Bibliographic documents for traditional use (30 years with 15 years in Europe)
Label and Marketing	• For TUHP, state folkloric claim "Traditionally used for relief of pain" and "Traditional application has not been evaluated by FDA" • For DS, a disclaimer "This product is not intended to diagnose, treat, cure, or prevent any disease"	• For DS, a disclaimer "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease"	• For THR, a certification mark and a statement that the product is exclusively based on long-standing use

The current DOH AO 53 s2015 Implementing Guidelines on the Promotion and Marketing of Prescription Pharmaceutical Products and Medical Devices, covers only prescription drugs and medical device not over-the-counter herbal medicines. The promotions and marketing of herbal medicines depends on the pharmaceutical company's strategy and financial capacity. The conventional 4Ps of marketing i.e. Product, Price, Placement and Promotion is still the main concept used by several companies. In terms of product, most companies rely on the concept of "natural remedy" as the main characteristic of the product. The NIRPROMP product use the government funded studies to back-up up their medical claim. Some companies marketing TUHP rely on anecdotal traditional use evidence and in some cases bordering to over-claim. Herbal medicines are supposed to address the rising cost of conventional medicine, but the cost of some herbal medicines is priced more than the synthetic preparations. The reason for this is that the raw materials of herbal medicines is more expensive than the synthetic raw materials.

Aside from product and pricing strategy, pharmaceutical companies also use a mix of promotion and marketing strategies depending on their strength and capacity. Companies with established relationship to medical doctors, professional societies use varied strategies to promote the product to prescribers. Ethical and some "not so ethical" promotions/marketing are being used. This mostly comes as a request by the prescribers. However, the DOH AO 53 s2015 is already being implemented and followed by pharmaceutical companies. For over-the-counter herbal medicines, direct to consumer marketing like media advertising, discounting or sampling to consumers etc. are being done. Digital marketing via social media, short message texting and e-mails are also increasing. Companies also have promotions and marketing activities to pharmaceutical distributors and retailers.

Post-marketing Regulation

After approval for marketing, there must be a methodological approach for post-marketing safety based on sales data and information on adverse drug reactions of newly introduced herbal medicinal products in the market.[11] The assumption that natural herbal medicines are generally safe may not have a strong basis. In China, about 10-15% of the ADR reports are related to traditional Chinese medicines mainly pertaining to the formulated products.[12] A well-designed pharmacovigilance system is therefore essential for developing reliable information on the safety of herbal medicines.

The existing systems were developed for synthetic medicines and require some modification to address the specific differences of medicinal herbs. One of the needed modifications may be the use of scientific plant names to standardize reporting of adverse events. Medicinal plants are different names and may therefore provide inaccurate estimates of adverse events.[13] There is also a need for traditional practitioners aside from medical practitioners to be part of the pharmacovigilance system. Appropriate guidance on these issues should may also be needed from FDA.[14]

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