FEATURE ARTICLE

Review of the Regulations for Clinical Research in Herbal Medicines in USA

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ABSTRACT In 2012, USA Food and Drug Administration (FDA) approved 39 new drugs, however, there are only two botanical drugs (one topical and one oral) approved by FDA since the publication of the FDA’s industry guidelines for the botanical drug product in June 2004. The approval shows the Western guideline can be used for herbal medicines, authors investigate current regulation on herbal medicine clinical research, identify challenges conducting clinical trials, and seek to produce some guidance for potential investigators and sponsors considering a clinical trial in this area. Key words were formulated for searching on Medline and FDA website to locate relevant regulations for clinical research in herbal medicines to understand current environment for herbal medicine usage and examine the barriers affecting herbal medicine in clinical trials. Authors critically explore case study of the 1st FDA approved botanical drugs, Veregen (sinecatechins), green tea leaves extract, a topical cream for perianal and genital condyloma. In consideration of current regulation environment in USA, based on the findings and analysis through the literature review and Veregen case study, authors produce and propose a Checklist for New Drug Application of Herbal Medicines for potential investigators and sponsors considering in a herbal medicine clinical trial.

KEYWORDS herbal medicine, Chinese medicine, clinical trial, traditional medicine, complementary medicine, review

Overview of Herbal Medicines in USA

The Food and Drug Administration (FDA) defined herbal medicines as botanical drug, available as (but not limited to) a solution (e.g., tea), powder, tablet, capsule, elixir, topical, or injection preparations consists of vegetable materials, which may include plant materials, algae, macroscopic fungi, combinations thereof, or may derived from plants or parts of plants, i.e. leaves, stems, buds, flowers, roots or tubers.1) Fermentation products and highly purified or chemically modified botanical substances are not considered as botanical drug by FDA.

Herbal medicine has been used as medicine for thousands of years,2) for example, saw palmetto was used for urinary symptoms in ancient Egypt,3) and a Chinese classic book named Inner Classic of the Yellow Emperor describes traditional Chinese medicines.4) Herbal medicines are popular in America: in the 19th century, around two-thirds of medicines listed in the first edition of the United States Pharmacopoeia (USP) published in 1820 were botanical substances,5) enter into 20th century, synthetic drugs were found to have larger pharmacologic effects and replaced herbal medicine in the United States.5) Currently only 120 conventional drugs in the USP are derived from plant Species,6,6) i.e., atropine is derived from Belladona (Atropa belladonna), codeine is derived from Poppy (Papaver somniferum), Digoxin is derived from Foxglove (Digitalis purpurea), etc. In the USA, around 2.5 % of adults were reported use of complementary and alternative medicine (CAM) in 1990,7) by 1997 a national survey showed 12.1% used CAMs in the previous year and this was up to 38.3% of adults and 11.8% of children in 2007,7,8) In response to increased

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public use of CAM, US Congress established the National Institutes of Health (NIH) Office of Alternative Medicine (OAM) in 1992. The NIH Office of Dietary Supplements was set up in 1994 to conduct researches in CAMs. In 1998, the NIH OAM was upgraded to the National Center for Complementary and Alternative Medicine (NCCAM). NCCAM is to evaluate mechanisms, efficacy and safety of botanical medicines through basic science studies, clinical research and the dedicated botanical research center was established. In 2004 order to benefit the public and protect the customer's safety and to provide the incentive of research and development for herbal medicine manufacturers, the USA FDA Centre for Drug Evaluation and Research (CDER) officially issued Guidance for Industry-Botanical Drug Products to facilitate development of new therapeutic class: botanical drug.

Regulation Environments Review in USA
Herbal (botanical) product which includes those already marketed in other countries as herbal medicines) can be categorized as following four classes: cosmetic, food, dietary supplements, or botanical drug under current regulation in the USA.

Cosmetic product is regulated by FDA Center for Food Safety and Applied Nutrition (CFSAN). For instance, Green tea and Aloe vera are among the commonly used ingredients in cosmetics.

Food is also regulated by FDA CFSAN, some herbs are marketed as food or spice, e.g. ginger, star anis, and garlic.

Most of herbs including those already marketed in other countries, i.e. China, are marketed as dietary supplements in the USA currently, provided that those products comply with the labeling requirements for dietary supplements.

In 1962, US Congress past the Kefauver-Harris Drug Amendment which require proof of safety and efficacy for all prescription and over-the-counter drugs but set herbal medicines to the category of food supplements. In the 1990s, FDA attempted to develop more strict regulations for herbal products, the Dietary Supplement Health and Education Act (DSHEA) was passed in 1994, the DSHEA defined dietary supplements as a product containing one or more of the following: a vitamin, mineral, amino acid, herb, other botanical, concentrate, metabolite, constituent, or extract. DSHEA placed dietary supplements in a distinct category from drugs. Labels of dietary supplements are required to state: "this product is not intended to diagnose, treat, cure, or prevent any disease." However, product labels are allowed to make health claims, such as "promotes prostate health" or "supports the circulatory system." According to the DSHEA, manufacturers of dietary supplements are not required to prove efficacy and safety prior to marketing, and also not required to report adverse events post marketing of the product. Alternatively if a CAM is to be marketed and intends to treat a specific disease, for example, to "cure", "treat", "mitigate", "prevent" common cold including its associated symptoms, then this product is treated with the same regulatory requirements as a prescription drug and will be subject to Investigational New Drug (IND) requirements.

CAM is reported frequently used as enhancing health and helping common chronic symptoms, such as arthritis, memory loss, fatigue, cancer, etc., which conventional medicine does not offer straightforward answers. CAM is attracting people who perceive nature as safe and healing. Bearing this concept in mind is the mistaken perception that a natural product is always safe. The studies, case reports, publication of adverse events and harmful drug-herb interactions had been frequently reported and prompted healthcare professionals, organizations and consumers call for more strict regulation on herbal medicines. In 2007, the US FDA issued new rules requiring Good Manufacturing Practices (GMPs) for dietary supplements to be phased in from 2008 to 2010. The new GMPs require dietary supplements be properly labeled and manufactured compliance with specified standards for personnel and equipment. Production controls and appropriate documentation are required by FDA.

Herbal medicines often have unique features, for example, "complex mixtures", "lack of a distinct active ingredient", and "substantial prior human use", hence in 2004, USA FDA CDER officially issued guidance for new therapeutic class: botanical drug. The Botanical Drug Guidance applies to only botanical product that intended to be developed and used as drugs. NCCAM and CDER have established the Botanical