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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,(5,6) 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 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.[1] 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.[9] 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."[8] 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,[9,10] CAM is attracting people who perceive nature as safe and healing.[11] Bearing this concept in mind is the mistaken perception that a natural product is always safe.[12] 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.[12] 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 Review Team to serve as a resource to all review divisions and offices in the Office of New Drugs (OND) in reviewing and evaluating INDs and New Drug Applications (NDAs) for botanical drug products.

Herbs have great potential for future medical research, around the globe, there are estimated 250,000 flowering plants, and over 85,000 plant species are documented for medical use,[13,14] up-to-date, only a small fraction of the plants have been studied for their therapeutic value.[15] In the USA only two botanical drugs have been approved. FDA's Industry Guidelines for the Botanical Drug Product were published in June 2004. The functions of herbs were identified through observation and experience following thousands of years of human using, but without clear understanding of mechanisms of action. The Western conventional medicines incorporated knowledge of anatomy, physiology and chemistry, it was developed through laboratory investigation primarily, thereafter the chemical compounds were identified and tested in animal models then in controlled trials on human subjects, phase Ⅰ, Ⅱ, Ⅲ and Ⅳ. Herbal medicine and conventional medicine differ in composition, the process of diagnosis and methods of treatment. Can current FDA regulations in drug development be applied to botanical drugs? What challenges encountered in conducting herbal medicine clinical trials? What should principal investigators (PIs) and sponsors take note of before pursuing a herbal drug trial?

Thus, this paper is seeking to: systematically evaluate the issues and challenges of undertaking clinical trials under FDA regulations; critically explore the case of the 1st FDA approved botanical drugs, Veregen (sinecatechins), green tea leaves extract. Then, based on the findings and analysis, author produces some guidance for sponsors and investigators if seeking to conduct trials under FDA regulations.

METHODS

A search strategy was developed to address the aims. The peer-reviewed articles identified through a search of academic databases, in addition, regulation guideline and FDA drug approvals and database were retrieved from FDA official website.

To identify relevant peer-reviewed articles, the literature searches were conducted in major biomedical databases Medline/EBSCO, EMBASE and CINAHL to understand current environment for Herbal medicine usage and examine the barriers affecting herbal medicine in clinical trials.

A number of key search terms and synonyms were identified to reflect the research question posed, "botanical drug", "herbal medicine", "traditional Chinese medicine", "traditional medicine", "phytotherapy", "regulation", "Clinical trial", "challenge", "safety". The searches were limited from 1 January 2002 to 31 December 2012. The following exclusion criteria were adopted: no abstract; abstract not in English; presentation as abstract only; editorials; letters; opinions; pharmacological studies. Also excluded were articles that do not address the research aims we examined.

Key words "Veregen" and "Botanical Drug" were formulated for searching on FDA official website to locate relevant regulations for clinical research in herbal medicines and data of Veregen Investigational New Drug IND application and NDA. Information of the first FDA approved botanical drug, Veregen (sinecatechins), green tea leaves extract, such as the approval history, letters, reviews, and related NDA documents of Veregen lodged into

FDA including approval letter(s), printed labeling, medical review(s), chemistry review(s), botanical review, pharmacology review(s), statistical review(s), clinical pharmacology, biopharmaceutics review(s) are critically explored and analyzed.

RESULTS

Issues and Challenges of Botanical Drug Trials

There are three main issues existed in herbal medicine research and development: quality, safety, and bias on herbal medicines.[15-20]

Quality Issue

There are multiple internal and external factors that may affect the chemical profile of the herbs. The quality of herbal medicine may vary during the different steps for development of herbal medicines starting from collection of raw materials to isolation of active ingredients, for instance, plant species used, place of cultivation, time of harvest in the season, photoperiod, climate, soil conditions, nutrient availability and moisture, storage condition, the part of the plant that was used, manufacturing process, and standardization.[18,19,21] The stages of manufacturing processes such as extraction, stability, shelf life and purity also play an importance role in deviation of chemical consistency and medicinal efficacy.[18]

Species of Plant

Some herbal medicines are used from closely related species. For example, echinacea is administrated for the treatment and prevention of the common cold, there are three species in the echinacea family that commonly used, Echinacea purpurea , or Echinacea pallida , or Echinacea angustifolia. But the biopharmacologic activity of these different species is uncertain. Thus serious injury may occur due to misidentification of other plant relative species and subsequent mislabeling.[18,19,22] In 1993, a Belgium clinic gave women slimming treatment with toxic herb Aristolochia fangchi instead of the anti-inflammatory herb Stephania tetrandra.[23,24] Over 100 of women suffered kidney failure after consumption of it. This tragedy is due to mistaken of botanical species and identity. The raw material was from China. In China, the term Fang Ji (防己) describes the roots of both Aristolochia fangchi and Stephania tetrandra. Belgium case highlighted the need for manufacturers to clearly state the scientific name of the herbal used rather than general name, the characteristics of herb shall be described in label to state the herbal medicinal products' Latin binomial, the part of the plant used, and the type of preparation.

Cultivation, Harvest and Storage Condition

The strength of a plant's pharmacologic activity may also vary depending on where it was planted and raised, when it was harvested, and the length of time it was stored.[19,25] Plant products and their active constituents can vary from year to year due to climatic changes involving rainfall, sunlight, and even genetic composition.[18,19,26] Prolonged storage may also lead to microbial contamination.

The Part of the Plant That Was Used

Different parts, i.e. leaves, stems, buds, flowers, roots or tubers, from the same plant species may have different pharmacologic activity. As an example, cinnamonmum cassia product function may be vary according to the plant parts used, branches or bark. The biochemical relationship and pharmacologic activity of these different parts of the same plant are unclear.[18,19]

Manufacturing Process

Herbs can be processed and formulated multiple ways. Herbs can be used as raw or extraction. A single

whole plant or various parts from multiple different plant species can be extracted through solvents, i.e., alcohol, glycerol, acetone, water, etc. These extracts can be in tablet form, or encapsulated, or made into liquid tinctures. Sometime whole herbs can also be eaten or consumed as teas, i.e., Chinese green tea, Japanese wheat tea. Topical applications can be produced using poultices or creams. Different processing techniques may lead to different chemical composition of the final product and also may modify the pharmacologic activity.[18,19]

Standardization and Consistency

Herbs are living organizations which contain complex substances and numberless of chemical constituents. For example, the medicinal plant Scutellaria baicalensis, contains more than 2000 chemicals.[27] Often it is uncertain which chemical constituent plays a primary role in the herbal pharmacologic activity. Thus identification of specific chemicals to be the active ingredients is difficult. Some herbal products are standardized to contain a specified amount of chemicals, for example, a number of compounds isolated from St. John's wort (Hypericum perforatum), naphthodianthrones (hypericin, pseudohypericin, protohypericin, protopseudohypericin, and cyclopseudohypericin), flavonoids (quercetin, rutin, and luteolin), hyperforin, several amino acids, and tannins,[28] initially St. John's wort was standardized to 0.3 percent hypericin, however, many experts did not agree hypericin is the most important component for antidepressant activity, subsequent studies shown that hyperforin modulate neurotransmitter levels including serotonin, norepinephrine, and dopamine.[29,30] Thus hyperforin may be in part from inhibition of neurotransmitter uptake rather than hypericin. Even when herbal products are labeled with standardized to certain percentage, the actual variation may be existed. Gilroy, et al[31] found that the amount of standardized content did not match the labeling in 47% of samples of Echinacea product on the market. Harkey, et al[32] reported a 15 to 200 fold variation in the concentration of two Ginseng biological ingredients: ginsenosides and eleuthrosides existed in 25 Ginseng products on the market. Thus it is difficult to ascertain the precise contents of the products patients are taking.

There is substantial variation in the quality of herbal products. Variability in herbal quality can impact the safety and efficacy of herbal medicine. In addition, uncertainty in quality and the poor-designed clinical studies make it difficult for health care professionals to proactively recommend clinical usefulness for public societies.

Safety Issue

Beside the adverse events caused by herbal quality variations, misusing species of plant, non-appropriate cultivation and storage, inferior manufacturing process, non-standardization of herb used, the drug-herb interactions and side effect of herb itself are two major safety issues.[15,17,33-35]

Adverse Effects

In the USA, the reports from various sources implicated that 10 to 68% of cases of drug-induced liver injury due to herbal and dietary supplements.[15,24] Additionally, there is no precise estimation of the prevalence of herbal induced hepatotoxicity, because patients often do not report the use of herbal products to their physicians.[36] For example, livery injury has been reported associated with the product named SlimQuick, extract of Camellia sinensis, Chinese green tea.[20,37-39] The mechanism of hepatocellular injury is unclear, but a genetic predisposition may be involved. Fortunately the liver injury can be resolved after discontinuation of the product.

Drug-herb Interactions

Two systematic reviews identified 51 and 1,491 unique herb-drug pairs that have been reported to involve herbal and dietary supplements (HDS) drug interactions.[33,35] Among the 152 identified HDS contraindications, the most frequent involved gastrointestinal (16.4%), neurological (14.5%), and renal/genitourinary diseases (12.5%).[35] Interactions between herb St. John's Wort and prescription or non-prescription drugs were the most

common source of adverse effects reported.[35,40,41] The hyperforin component of St. John's wort induces the CYP3A4 system which metabolizes a number of drugs including protease inhibitors, cyclosporine, oral contraceptives, irinotecan, warfarin, and digoxin, the concomitant use of St. John's Wort with these drugs will cause treatment failure.[22,35,42-48]

Bias on Herbal Medicine

Herbal products are often used by patients at their own discretion and without the input of their physicians,[49-51] FDA regulations require dietary-supplement manufacturers to evaluate the identity, purity, strength, and composition of their products. But these requirements are not designed to demonstrate product efficacy and safety, thus physicians do not recommend herbal therapies for most patients.[50,51] Herbal medicine has been criticized in Eastern and Western, "The medical practice of traditional medicine is a process of trials and error, and concerns the understanding and control of herbs from the Chinese Materia Medica, the philosophical theories were created afterwards to provide the explanatory framework for the practices, and are used to win the patients' trust." Says Zhang Da-qing, director of the Centre for History of Medicine at Peking University in China.[52] When NIH spent US$125 million on NCCAM for CAM research in 2009, many US scientists complained the funding is a waste of money and time. Steven Novella, a neurologist at Yale University says, "You are doing scientific research on treatment modalities that are not being used or promoted by science-based practitioners in the first place, scientific evidence shows that it doesn't work. So what's the point?"[53] Marcus, a scientist from the Institute for Science in Medicine critique the government policies promoting alternative medicine, commented NCCAM as "a remarkable waste of money", "the best thing they could do with the NCCAM is to dissolve it."[53] Indeed, 5 years plan, Third Strategic Plan 2011–2015, published by NCCAM has a greater focus on symptom management and mind-body medicine instead of herbal therapies.

DISCUSSION

Veregen Ointment 15% contains one molecular entity named sinecatechins and indicates for topical treatment of external genital and perianal warts, it is an extract of great tea leaves, a single part of a single plant. The drug substance in Veregen is sinecatechins, formally named Kunecatechins, which is a partially purified fraction of the water extract of green tea leaves from Camellia sinensis (L.) O Kuntze, and is a mixture of catechins and other green tea components. Catechins constitute 85% to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg), and some additional minor catechin derivatives i.e. Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined botanical constituents derived from green tea leaves.

Veregen is the first NDA approval for a botanical product since the drafting of the botanical guidance. It provided a path towards development, approval and marketing of future herbal medicines.[54] Several unique issues were extensively discussed and considered by Botanical Review Team (BRT) in the NDA of Veregen. These included how to adequately demonstrate identification and control of the botanical raw material, how to demonstrate adequate characterization of the drug substance, how to ensure the therapeutic consistency of marketing batches, how to name the drug substance, and how to evaluate the pharmacodynamics/pharmacokinetics for a product with multiple active ingredients. Each of these issues was addressed and resolved adequately by the review team for this drug product.

Plant Chemistry and Cultivation

Botanical drug substances are multi-component mixtures. The quality and quantity of components highly depend on variation in the raw materials or manufacturing process. To ensure consistency and quality of the plant

substance, the starting raw material must be precisely identified, including the control of the location, growing conditions, and harvesting methods for the plant. The manufacturing procedure that processed the raw materials into the final product must be controlled, therefore the individual components in the multi-component mixture can be remained consistent between batches.

During the Veregen NDA, the botanical review team worked with the sponsor to ensure that the tea variety/cultivars for Camellia sinners (L.) O. Kuntze were identified and controlled in the to-be-marketed product. The active ingredient in this drug substance is not identified and the entire drug substance is determined to be active. In order to ensure the therapeutic efficacy of individual and future batches of the drug substance, the NDA review team collaboratively determined that using the established cultivars from the drug development program would be important for maintaining consistency of the botanical raw material and the botanical drug substance. Any introduction of new variaties/cultivars should be pre-approved by the agency before production of marketing batches, and agency review/approval is needed for changing the suppliers of botanical raw materials. Such control, FDA emphasized is to ensure minimize the variability of the botanical chemical composition at the plants biological and raw material level.[16]

The Botanical Guidance clearly states that both purification and identification of the active ingredients in botanicals are optional and not required. Referring to the Veregen approved label, the active ingredient is called sinecatechins which is a partially purified fraction of the water extract of green tea leaves. This active ingredient encompasses 85% to 95% (by weight) of catechins and unknown rest. Hence FDA regulation concern in plant chemistry, manufacturing and quality control instead of purification and identification of active ingredients.

In consideration of plant biology and herbal raw material, the FDA BRT recommends that International or local Good Agricultural Practice (GAP) procedures, for example, WHO Guidance on Good Agricultural and Collection Practices (GACP) for Medicinal Plants, GAP for Traditional Chinese Medicine, China, are to be followed in addition to the tea growing guideline issued by the local authority for tea production for food/beverage uses, as appropriate. BRT believes through proper raw material control and manufacturing controls and specifications, drug product and clinical effect consistency is expected to be meet with no major practical difficulties. As there is no independent biological assay available to estimate the activity of the drug substance, acceptance criteria for Veregen substance are designed to reflect the clinical batches used to demonstrate safety and efficacy. Flowing extensive discussion, agreement was reached between the sponsor and the FDA regarding the allowable specification profile for the to-be-marketed Veregen formulation. The approval of Veregen NDA application includes agreements by the sponsor to comply with the raw materials, processing and manufacturing controls agreed upon during the review process. If any deviation from the specifications of Veregen substance used in the clinical trial incurred, FDA will request additional clinical studies with such new substance.

Manufacturing Controls

Batch-to-batch consistency is addressed extensively in FDA BRT review. The amounts of each catechin may vary from batch to batch used for manufacturing the drug product. In order to determine how to control the amount of each component, data analysis was performed by FDA. FDA proposed that, acceptance criteria is based on the amounts contained in clinical trial batches which were determined to be efficacious. Thus an in-house analysis of the drug substance batches used in the drug product batches for clinical trials and stability was performed and an acceptance criterion for individual catechins, total catechins and other unidentified components of drug substance was proposed. Agreement on these criteria is reached between FDA and sponsor. The acceptance criteria of particle size of drug substance has also been included in the drug substance specifications. The acceptance criteria for the drug substance batches are linked to demonstration of clinical efficacy via the clinical trials presented in the application.

Nonclinical and Clinical Study

Botanical Guidance stipulates that the assessment of safety for preliminary clinical studies has relied on past human experiences documented in literature and reference compendia, including previous clinical studies, historical use of the botanical ingredients in alternative medicine or recent marketing as dietary supplements. There is an extensive researching literature on green tea. FDA fully considered adverse events gastrointestinal symptoms associated with green tea extracts, thus Veregen 15% ointment was tested for up to 3 months orally or topically in rats and dogs and for up to 9 months topically in mini-pigs. The sponsor conducted a full pharmacology and nonclinical toxicology study and observed no safety problems.

For clinical trial to support FDA drug approval, there is no difference of the regulatory requirements between botanical drug and conventional Western drug. The efficacy of Veregen was tested in two randomized placebo controlled and multicenter trials conducted in the USA and foreign countries. The complete clearance of external genital and perianal warts was used as the endpoints. Clinical outcome showed there was no significant difference between the two doses 10% and 15%. Thus FDA had adequate assurance of the therapeutic consistency of future Veregen batch as dose response curve is flat, therefore the variations within the Veregen drug substances may not be crucial to the therapeutic response.[16]

Recommendations

If the sponsor and investigators would like to pursue a botanical drug NDA, and the botanical drug investigated contains a single herb like Veregen. In consideration of the modern era of FDA regulation environment, based on the findings and analysis of Veregen approval documents released by FDA, authors produced guidance in three perspectives: clinical trial design, clinical trial reporting and chemistry and manufacturing control for sponsors and investigators.

Clinical Trial Design

Clinical trial sponsor and principal investigator (PI) need to rethink the way herbal medicine is tested. Herbal RCTs design may need to consider individual pharmacogenomics. For instance, an anti-lung-cancer drug named gefitinib which inhibits epidermal growth factor receptor (EGFR) signaling in target cells, provides patients longer cancer remission period and fewer side effects than conventional chemotherapy.[55] But only patients with a specific mutation in the gene that encodes EGFR get benefit most from gefitinib. Initial RCTs showed no effectiveness because none of the subjects in the trial was included based on EGFR activity, but RCTs results are positive response only after EGFR subgroups were identified.[56,57] These types of RCTs include patients according to their genotype rather than the traditional methods based on clinical diagnosis. This personalized medicine may be corresponding well to individualized diagnostic and individualized treatment concept of traditional Asia medicine, i.e., Van, et al[58-60] study showed that "heat" and "cold", two Chinese medicine diagnosis patterns, was associated with different underlying genomic and metabolomics profiles and different treatment outcomes. Thus sponsor and PI need to consider alternative therapeutic endpoint for RCTs design, redesigning RCTs may integrate traditional herbal medicinal approaches to conventional Western medicine. For example, in a patient with high cholesterol, using garlic or soy supplements, which reduce total cholesterol by approximately 4%–6%, is relatively lower in comparison with the use of statin drugs, which reduce cholesterol by 17%–32%.[61] But in long-term symptom management, garlic or soy supplements may become a good option as it is risky free product compare with drugs in a long-term use.

Clinical Trial Reporting

The CONsolidated Standards Of Reporting Trials Statement (CONSORT) framework is an international collaboration project and solely designed to assist investigators and authors on the necessary information to be included in reports of controlled clinical trials.[62] In 2004, a group of clinical trial experts,

pharmacologists and methodologists, developed the herbal medicine trial guidelines add into current CONSORT items to aid editors and reviewers in assessing the validity and reproducibility of herbal medicinal product trial.[62] The CONSORT Herbal Intervention version highlight information suggested in RCTs reports of herbal medicine.[62] For example, herbal medicines vary by part of plant used, the type of extract (aqueous, alcoholic, glycerin), and delivery form, two different extract methods of the same botanical plant species may have different phytochemical properties or different pharmacokinetic effect. Thus the above information of characteristics of the herbal product used is required to provide reviewers with scientific data of intervention. For instance, CONSORT Herbal Intervention Checklist Item 1 request stating the herbal medicinal products' Latin binomial, the part of the plant used, and the type of preparation, the Checklist Item 4A request the Latin binomial name together with botanical authority and family name for each herbal ingredients, the proprietary product name or the extract name and the name of the manufacturer of the product,[62] sponsor and investigators who are pursuing herbal medicine RCTs are encouraged to familiarize themselves with the recommendations presented in the CONSORT Herbal Intervention version at the time when they plan the clinical study. The specific issue has to be addressed in regards of botanical drug trials, the detailed description of herb shall be provided, eg, species of plant, the part of the plant that was used, herbal product name, characteristics of the herb, dose and quantitative description, qualitative testing, placebo group. Prior to conducting the study, a thorough literature search shall be performed, as there is many studies may have been conducted in foreign countries and published in non-English language. PI may have to look into specific interactions of herbal with conventional drugs, the drug interaction tool (Lexi-Interact™ Online) can be one of the good database for herbal-drug interaction safety concern.

Chemistry and Manufacturing Control

Chen, et al[16] who are in the FDA botanical review team state whether the future marketed batch of botanical drugs would have the same efficacious as that observed in clinical trial is the main concern for FDA for approval of herbal drug. Although plant growth can be affected by environment factors, soil, weather, location, season, etc., adequate raw material quality control can be able to achieved. For example, FDA BRT and Botanical Guidance recommend following International or local GAP procedures, WHO Guidance on GACP for Medicinal Plants, GAP for Traditional Chinese Medicine, China. Some other useful measures recommended by Botanical Guidance are fingerprinting, conducting chromatographic analyses of marker compounds and developing clinically relevant bioassays to quantity their activity. These analytical technologies would ensure therapeutic consistency of future botanical drug batch if all or most active ingredients of herbal medicine are recognized. However the active ingredients of many herbal products are either uncertain or unknown, if such difficulties exist, Botanical Guidance recommended developing clinically relevant bioassays because such bioassays provide a measure of overall potency that would ease many aspects of new drug development and greatly facilitate quality control in post-approval manufacturing.[16]

Multi-Plants Botanical Drug

In order to benefit the public health and protect the customers' safety as well, provide the incentive of research and development in herbal medicine, FDA released a new Guidance for Industry-Botanical Drug Products to demonstrate its safety and efficacy through well-designed clinical trials and approved the first botanical drug. It is expected to have more botanical drugs and tighter competition in the near future. However, Guidance for Industry Botanical roducts does not describe if the contribution of each herb in the formula shall be demonstrated. For the herbal formula containing more than four components, the clinical trials can become very large to demonstrate the effectiveness of either single plant alone or in combination with other plants. Moreover demonstration of a significant effect of each ingredient is very challenging.[16] How does FDA consider and review the multiple-plant herbal medicine application? There is no preceding successful case for reference. Herewith authors are unable to give any advice based on current regulatory environment. However, CDER BRT did mention

this challenging faced by FDA,[16] perhaps there is no universal formula to apply on multi-herb botanical drug NDA at his moment and such IND is to be reviewed case by case. CDER BRT suggests that sponsor and investigators should consult with BRT in this issue before they proceed to IND application for a specific multi-herb drug to seek guanidine and consolation. BRT is established in February 2003, it provides scientific expertise on botanical issues to the reviewing staff and ensures consistent interpretation of the Guidance for Industry- Botanical Drug Products. The BRT also provides assistance to sponsors of botanical applications in the interpretation of the regulation and their interaction with the FDA.

Recommendation

In consideration of current regulation environment in the USA, based on the findings and analysis through the literature review and Veregen case study, authors produced and proposed a Checklist for New Drug Application of a Herbal Medicine (Table 1) for potential investigators and sponsors considering in a herbal medicine clinical trial.

Table 1. Proposed Checklist for New Drug Application of A Herbal Medicine

Item	Descriptor
1	The Latin binomial name and family name and common name for each herbal ingredient.
2	The proprietary product name (i.e., brand name) or the extract name (e.g., Abc-11) and the name of the manufacturer of the product.
3	The part(s) of plant used to produce the product or extract.
4	The type of product used [e.g., raw (fresh or dry), extract.
5	The type and concentration of extraction solvent used (e.g., 80% ethanol, 100% H2O, 90% glycerine) and the herbal drug to extract ratio (drug:extract; e.g., 2:1)
6	The starting raw material of the product must be precisely identified. (e.g. cultivars used, plant varieties used, control of the location, growing conditions, harvesting methods for the plant, International or local Good Agricultural Practice GAP procedures applied)
7	Product's chemical fingerprint and methods used (equipment and chemical reference standards) and who performed it (e.g., the name of the laboratory used). Whether or not a sample of the product (i.e., retention sample) was retained and if so, where it is kept or deposited.
8	Description of any special testing/purity testing (e.g., heavy metal or other contaminant testing) undertaken. Which unwanted components were removed and how (i.e., methods).
9	Standardization: what to (e.g., which chemical component(s) of the product) and how (e.g., chemical processes or biological/functional measures of activity).
10	Previous nonclinical & clinical study. (e.g., what prior nonclinical & clinical study have done on product if any, what evidence does the literature shown)
11	Clinical trial reporting format. (e.g., The CONsolidated standards of reporting trials statement CONSORT herbal intervention version)
12	If a multi-plants ingredients botanical drug to be investigated as investigational new drug IND application, FDA CDER Botanical Review Team BRT recommend sponsor go for consolation before proceeding IND.

If herbal medicines are to be accepted as botanical drugs, their quality needs to be standardized and rigorous scientific data on their efficacy and safety must be supplied. Only fulfill this then herbal medicine can be integrated into a global health-care system.

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