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# On Clinical Development of Traditional Chinese Herbal Medicine

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## ABSTRACT

In recent years, the slowdown of new drug development has resulted in search for alternative medicines such as traditional Chinese herbal medicine (TCM) that can treat critical and/or life-threatening diseases in the medical community and pharmaceutical industry. Although the development of promising traditional Chinese herbal medicine has great potential, it has been challenged regarding how to effectively and scientifically develop and evaluate a promising TCM under investigation due to the fact that there are some fundamental differences between a Western medicine and a TCM. This article provides a comprehensive review of critical issues that are commonly encountered during the development of a TCM. These issues include, but are not limited to, variation (or consistency) in raw materials, component-to-component interactions, animal studies, matching placebo and calibration of study endpoints in clinical trials, packaging insert, and transition from experience-based to evidence-based clinical practice and investigation.

**Keywords:** Chinese herbal medicine; Test for consistency; Flexible dose; Matching placebo; Evidence-based clinical investigation; Global dynamic balance or harmony;

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## 1. INTRODUCTION

In recent years, as more and more innovative drug products are due expiration of patent protection and the slowdown of new drug development, the search for alternative medicines such as traditional Chinese herbal medicine that can treat critical and/or life-threatening diseases has become the center of attention of many research organizations such as the United States National Institutes of Health (NIH) and pharmaceutical industry. This leads to the development of botanical drug product or Chinese herbal medicine, especially for those intended for treating critical and/or life-threatening diseases such as cancer. The alternative medicines include, but are not limited to, botanical drug product and traditional Chinese herbal medicine. In this article, we will refer to Chinese herbal medicine as traditional Chinese medicine (TCM). The use of TCM in humans for treating various diseases has a history of several thousand years, although limited convincing scientific evidence (documentations) regarding clinical safety and efficacy are available. Thus, how to effectively and scientifically develop a promising TCM has become an important issue in pharmaceutical and/or clinical development.

A Western medicine (WM) is referred to as a small molecular chemical drug product that often contains a *single* active ingredient. In practice, adequate and well-controlled, randomized clinical trials are conducted for obtaining substantial evidence of clinical safety and efficacy for the WM under investigation. Unlike a WM, a TCM usually consists of *multiple* active components, which are difficult, if not impossible, to be characterized and their relationships are often unknown. Thus, for pharmaceutical and/or clinical development of a TCM, it is of great concern whether a TCM can be scientifically evaluated the Western way due to some fundamental differences between WMs and TCMs. The Western way is to follow the process of investigational new drug application (IND) and new drug application (NDA) for review and approval of a regulatory submission of a drug product under investigation (see, e.g., MOPH, 1992; WHO, 1998: DOH, 2004a,b; FDA, 2004). These fundamental differences include differences in medical theory, mechanism, perception, and practice, diagnostic procedures (e.g., inspection, auscultation and olfaction, interrogation, and pulse taking and palpation), criteria for evaluation of safety and efficacy in clinical trials, treatment (i.e., fixed dose for a Western medicine versus a flexible dose for a TCM), and objective evidence-based approach for WMs versus subjective experience-based approach for TCMs (see, e.g., Chow, Pong, and Chang, 2006; Chow, 2015; Chow and Song, 2015).

The purpose of this article is multi-fold. First, it is to provide a comparison between a WM (e.g., chemical drug product) a traditional TCM (e.g., botanical drug product) in terms of the fundamental differences. Second, it is to outline the potential and promise of TCM development. Finally, it is to discuss critical scientific and/or regulatory issues that are commonly encountered during the development of a TCM. These issues include, but are not limited to, variation (or consistency) in raw materials, component-to-component interactions, animal studies, matching placebo and calibration of study endpoints in clinical trials, packaging insert, and transition from experience-based to evidence-based clinical practice. In the next section, major fundamental differences between a WM and a TCM are outlined. Section 3 discusses regulatory and clinical perspectives regarding the development of a promising TCM. Critical issues that are commonly encountered in development of a promising TCM are described in Section 4.

## 2. FUNDAMENTAL DIFFERENCES BETWEEN WM AND TCM

The process for pharmaceutical/clinical research and development of WMs is well established, and yet it is a lengthy and costly process (Chow and Liu, 2013). This lengthy and costly process is necessary to ensure the efficacy, safety, purity, quality, stability and reproducibility of the drug product under investigation. For pharmaceutical/clinical research and development of a TCM the Western way, one may consider directly applying this well-established process to the development of a TCM under investigation. However, this process may not be feasible due to some fundamental differences between a TCM and a

WM, which are summarized in Table 1. These fundamental differences including (1) medical theory, mechanism, perception, and practice, (2) diagnostic procedure, (3) treatment, (4) evidence-based versus experience-based clinical practice, and (5) regulatory perspectives are briefly described in the subsequent subsections.

### 2.1 Medical Theory/Mechanism and Perception/Practice

**Medical theory and mechanism** – TCM is a 3000-year-old holistic medical system encircling the entire scope of human experience. It combines the use of Chinese herbal medicines, acupuncture, massage, and therapeutic exercise such as *Qi-Gong* (the practice of internal *air*) and *Tai-Chi* for both treatment and prevention of disease. With its unique theories of etiology, diagnostic systems, and abundant historical literature, TCM itself consists of Chinese culture and philosophy, clinical practice experience, and the use of many medical herbs.

As indicated by Chow, Pong, and Chang (2006), Chinese doctors believe how a TCM functions in the body is based on the eight principles, five-element theory, five *Zang* and six *Fu*, and information regarding channels and collaterals. Eight principles consist of *Yin* and *Yang* (i.e., negative and positive), cold and hot, external and internal, and *Shi* and *Xu* (i.e., weak and strong). The eight principles help Chinese doctors to differentiate syndrome patterns. For instance, people with *Yin* will develop disease in a negative, passive, and cool way (e.g., diarrhea and back pain), while people with *Yang* will develop disease in an aggressive, active, progressive, and warm way (e.g., dry eyes, tinnitus, and night sweats). The five elements (earth, metal, water, wood, and fire) correspond to particular organs in the human body. Each element operates in harmony with the others. The five *Zang* (or *Yin* organs) include heart (including the pericardium), lung, spleen, liver, and kidney, while the six *Fu* (or *Yang* organs) include gall bladder, stomach, large intestine, small intestine, urinary bladder, and three cavities (i.e., chest, epiastrium, and hypogastrium). *Zang* organs can manufacture and store fundamental substances. These substances are then transformed and transported by *Fu* organs. TCM treatments involve a thorough understanding of the clinical manifestations of *Zang-Fu* organ imbalance, and knowledge of appropriate acupuncture points and herbal therapy to rebalance or maintain the balance of the organs. The channels and collaterals are the representation of the organs of the body. They are responsible for conducting the flow of energy and blood through the entire body. The elements of TCM can also help to describe the etiology of disease including six exogenous factors (i.e., wind, cold, summer, dampness, dryness, and fire), seven emotional factors (i.e., anger, joy, worry, grief, anxiety, fear, and fright), and other pathogenic factors. Once all of the information are collected and processed into a logical and workable diagnosis, the traditional Chinese medical doctor can determine the treatment approach.

Under the medical theory and mechanism described above, Chinese doctors believe that all of the organs within a healthy subject should reach the so-called *global dynamic balance or harmony* among organs. Once the global balance is broken at certain sites such as heart, liver or kidney, some signs and symptoms then appear to reflect the imbalance at these sites. An experienced Chinese doctor usually assesses the causes of global imbalance before a TCM with flexible doses is prescribed to fix the problem. This approach is sometimes referred to as a personalized (or individualized) medicine approach.

**Medical Perception and Practice** – Different medical perceptions regarding signs and symptoms of certain diseases could lead to a different diagnosis and treatment for the diseases under study. For example, the signs and symptoms of type 2 diabetic subjects could be classified as the disease of *thirsty reduction* by Chinese doctors. The disease of type 2 diabetes is not recognized by Chinese medical literature although they have the same signs and symptoms as the well-known disease of thirsty reduction. This difference in medical perception and practice has an impact on the diagnosis and treatment of the disease.

In addition, we tend to see therapeutic effect of WMs sooner than TCMs. In many cases, however, acupuncture in conjunction with cupping treatment is found to be very effective

for patients with frozen shoulder, acute back sprain and ankle twist. In practice, TCMs are often considered for patients who have chronic diseases or non-life-threatening diseases. For critical and/or life-threatening diseases such as cancer or stroke, TCMs are often used as the second line or third line treatment with no other alternative treatments. In many cases such as patients with later phase of cancer, TCMs are often used in conjunction with WMs without the knowledge of the primary care physicians.

### 2.2 Diagnostic Procedures

Chinese diagnostic procedure for patients with certain diseases typically consists of four major techniques, namely, inspection, auscultation and olfaction, interrogation, and pulse taking and palpation. All these diagnostic techniques are not only to provide objective basis for differentiation of syndromes, but also to collect information regarding signs and symptoms from the patient. *Inspection* involves observingthepatient's general appearance (strong or weak, fat or thin), mind, complexion (skin color), five sense organs (eye, ear, nose, lip, and tongue), secretions, and excretions. *Auscultation* focuses listening to the voice, expression, respiration, vomit, and cough. *Olfaction* involves smelling the breath and body odor. *Interrogation* is to ask questions about specific symptoms and the general condition including history of the present disease, past history, personal life history, and family history. *Pulse taking and palpation* can help to judge the location and nature of a disease according to the changes of the pulse. The four Chinese diagnostic procedure is subjective, with large between rater variability (i.e., variability from one Chinese doctor to another). This subjectivity and variability will have an impact not only on the patient's
evaluability but also the prescribability of TCM, which will be further discussed below.

**Objective versus subjective criteria for evaluability –** For evaluation of a WM, objective criteria based on some well-established clinical study endpoints are usually considered. For example, response rate (i.e., complete response plus partial response based on tumor size) is considered a valid clinical endpoint for evaluating clinical efficacy of oncology drug products. Unlike WMs, Chinese diagnostic procedure for evaluation of a TCM is very subjective. The use of a subjective Chinese diagnostic procedure has raised the following issues. First, it is a concern whether the subjective Chinese diagnostic procedure can accurately and reliably evaluate clinical efficacy and safety of the TCM under investigation. Thus, it is suggested that the subjective Chinese diagnostic procedure should be validated in terms of its accuracy, precision, and ruggedness before it can be used in TCM clinical trials. A validated Chinese diagnostic procedure should be able to detect a clinically significant difference if the difference truly exists. On the other hand, it is not desirable to wrongly detect a difference when there is no difference.

In clinical trials, evaluation is usually based on some validated tools (instruments) such as laboratory tests. Test results are then evaluated against some normal ranges for abnormality. Thus, it is suggested that the Chinese diagnostic procedure must be validated in terms of validity and reliability, and its false positive and false negative rates, before it can be used for evaluation of clinical efficacy and safety of the TCM under investigation.

### 2.3 Treatment

TCM prescriptions typically consist of a combination of several components. The combination is usually determined based on the medical theory of global dynamic balance (or harmony) among organs, and the observations from the Chinese diagnostic procedure. The use of Chinese diagnostic procedure is to find out what caused the imbalance among these organs. The treatment is to re-install the balance among these organs. Thus, the dose and treatment duration are flexible in order to achieve the balance. This concept leads to the concept of so-called personalized (or individualized) medicine, which minimizes intra-subject variability.

**Single active ingredient versus multiple components** – Most WMs contain a single active ingredient. After drug discovery, an appropriate formulation (or dosage form) is necessarily developed so that the drug can be delivered to the site action in an efficient way. At the same time, an assay is necessarily developed to quantitate the potency of the drug. The drug is

then tested on animals for toxicity, and humans (healthy volunteers) for pharmacological activities. Unlike the WMs, TCMs usually consist of multiple components with certain relative proportions among the components. As a result, the typical approach for evaluation of single active ingredient for WM is not applicable.

In practice, one may suggest evaluating the TCM component by component. However, this is not feasible due to the following difficulties. First, in practice, analytical methods for quantitation of individual components are often not tractable. Thus, the pharmacological activities of these components are not known. It should be noted that the component which comprises the major proportion of the TCM may not be the most active component. On the other hand, the component that has the least proportion of the TCM may be the most active component of the TCM. In practice, it is not known which relative proportions among these components can lead to the optimal therapeutic effect of the TCM. In addition, the relative component-to-component and/or component by food interactions are usually unknown, which may have an impact on the evaluation of clinical efficacy and safety of the TCM.

**Fixed dose versus flexible dose** –Most WMs are usually administered in a fixed dose (say a 10 mg tablets or capsule). On the other hand, since a TCM consists of multiple components with possible varied relative proportions among the components, a Chinese doctor usually prescribes the TCM with different relative proportions of the multiple components based on individual patient's baseline characteristics such as age, height, weight, and severity of the sign and symptom of the individual patient according to his/her best judgment following a subjective evaluation based on the Chinese diagnostic procedure. Different relative proportions could result in different therapeutic effects for similar but different indications. Thus, unlike a WM which is prescribed as a fixed dose, a TCM is often prescribed as an individualized flexible dose.

The approach of WM with a fixed dose is a population approach to minimize the between subject (or inter-subject) variability, while the approach to TCM with an individualized flexible dose is to minimize the variability within each individual. In practice, it is a concern whether an individual flexible dose is compatible with a Western evaluation of the TCM. An individualized flexible dose depends heavily upon the Chinese doctor's subjective judgement, which may vary from one Chinese doctor to another. As a result, although an individualized flexible dose does minimize intra-subject variability, the variability from one Chinese doctor to another (i.e., the doctor-to-doctor or rater-to-rater variability) could be huge, and hence non-negligible.

### 2.4 Experience-Based versus Evidence-Based Clinical Practice

TCMs have been in practice for thousands of years. Many of the commonly used TCMs were found safe and efficacious. However, evidence of safety and efficacy of these TCM were not documented for scientific evaluation. Unlike evidence-based clinical data, the experience-based clinical information has been criticized for lacking of scientific validity and reliability for assessment of safety and efficacy of the TCMs (currently being used or under development). As an example, Chinese patients are likely to report only successful cases, while those patients who fail (which may be due to severe adverse events or lack of efficacy) are likely seeking for alternatives and then lost to follow-up. As a result, experience-based clinical information is considered not only subjective, but also biased (due to selection bias) and misleading.

In practice, how to collect relevant and important clinical data from experience-based clinical practice is then of particular interest to clinical scientists for development of TCMs. Most Chinese doctors resist to (1) collect clinical data that they are not familiar with, and (2) cooperate with Western doctors to collect further information from their patients due to fundamental differences in culture and clinical theory, perception, and practice. Thus, the transition from experience-based clinical practice to evidence-based clinical practice requires careful communication and planning. This transition is essential for achieving the ultimate goal of modernization and/or Westernization of TCMs.

## 3. REGULATORY/CLINICAL PERSPECTIVES

In pharmaceutical/clinical development, before a TCM clinical trial is conducted, the following questions are often asked.

(1) Will the TCM clinical trial be conducted by Chinese doctors alone, Western clinicians alone, Western clinicians who have some background of Chinese herbal medicine alone, or both Chinese doctors and Western clinicians?
(2) Will traditional Chinese diagnostic and/or trial procedures be used throughout the TCM clinical trial?
(3) Upon approval, is the TCM intended for use by Chinese doctors or Western clinicians?

With respect to the first two questions, if the TCM clinical trial is to be conducted by Chinese doctors alone, the following questions arise. First, should the Chinese diagnostic procedure be validated in order to provide an accurate and reliable assessment of the TCM? In addition, it is of interest to determine how an observed difference obtained from the Chinese diagnostic procedure can be translated to the clinical endpoint commonly used in similar WM clinical trials with the same indication. These two questions can be addressed statistically by the calibration and validation of the Chinese diagnostic procedure with respect to some well-established clinical endpoints for evaluation of Western medicines. If the TCM clinical trial is to be conducted by Western clinicians or Western clinicians who have some background of Chinese herbal medicine, the standards and consistency of clinical results as compared to those WM clinical trials are ensured. However, the good characteristics of TCM may be lost during the process of the conduct of the TCM clinical trials. On the other hand, if the TCM clinical trial is to be conducted by both Chinese doctors and Western clinicians, difference in medical practice and/or possible disagreement regarding the diagnosis, treatment, and evaluation are major concerns. For the third question, if the TCM is intended for use of Chinese doctors but it is conducted by Western clinicians, difference in perception regarding how to prescribe the TCM is of great concern. The preparation of a package insert based on the clinical data could be a major issue, not only to the sponsor but also to regulatory authorities. Similar comments apply to the situation where the TCM is intended for use of Western clinicians, but the trial is conducted by Chinese doctors.

As a result, it is suggested that the intention of use (i.e., labeling for the indication) be clearly evaluated when planning a TCM clinical trial. In other words, the sponsor needs to determine whether the TCM is intended for use of Western clinician only, Chinese doctors only, or both Western clinicians and Chinese doctors at the planning stage of a TCM clinical trial, for an adequate package insert of the target diseases under study.

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**Table 1. Fundamental Differences between a WM and a TCM**

| Description | Western Medicine | Traditional Chinese Medicine |
|---|---|---|
| Active ingredient | Single | Multiple |
| Dose | Fixed | Flexible |
| Diagnostic procedure | Objective; Validated | Subjective; Not validated |
| Therapeutic index | Well-established | Not well-established |
| Release of symptoms | Quick | Slow |
| Medical theory and mechanism | Specific organs | Global dynamic balance/harmony among organs |
| Medical perception and practice | Evidence-based | Experience-based |
| Statistics | Population | Individual (personalized) |

**Table 1. Full $2^4$ Factorial Design**

| | Design matrix | | | | |
|---|---|---|---|---|---|
| Run | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $Y$ |
| 1 | − | − | − | − | $Y_1$ |
| 2 | + | − | − | − | $Y_2$ |
| 3 | − | + | − | − | $Y_3$ |
| 4 | + | + | − | − | $Y_4$ |
| 5 | − | − | + | − | $Y_5$ |
| 6 | + | − | + | − | $Y_6$ |
| 7 | − | + | + | − | $Y_7$ |
| 8 | + | + | + | − | $Y_8$ |
| 9 | − | − | − | + | $Y_9$ |
| 10 | + | − | − | + | $Y_{10}$ |
| 11 | − | + | − | + | $Y_{11}$ |
| 12 | + | + | − | + | $Y_{12}$ |
| 13 | − | − | + | + | $Y_{13}$ |
| 14 | + | − | + | + | $Y_{14}$ |
| 15 | − | + | + | + | $Y_{15}$ |
| 16 | + | + | + | + | $Y_{16}$ |

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## 4. CRITICAL ISSUES IN TCM DEVELOPMENT

In this section, a number of critical issues that are often encountered during the development of a TCM are briefly discussed.

### 4.1 Variation in Raw Materials

One of the critical issues in TCM manufacturing is variation in raw materials. The variation in raw materials, which may be due to the fact that they come from different regions, climates, and time of harvest, could have a negative impact on the quality of the TCM and consequently the safety and efficacy of the TCM. Yan and Qu (2013) indicated that the efficacy of a TCM depends upon the combined effects of its components. Variation in chemical composition between batches of TCM has been always the deterring factor of achieving consistency in efficacy. These components, however, may or may not be correlated and may have component-to-component interaction which will have an impact on achieving optimal therapeutic effect of the TCM. In practice, unfortunately, the correlations among the components and their relative ratios for achieving optimal therapeutic effect are often unknown.

**Utilization Ratio of Extracts (URE)** –Yan and Qu (2013) indicated that batch mixing process can significantly reduce the batch-to-batch variation in TCM extracts by mixing them in a *well-designed* proportion, which is referred to as utilization ratio of the extracts (URE). Yan and Qu (2013) suggested an innovative and practical batch mixing method for achieving an acceptable efficiency for manufacturing of TCM products by using a minimum number of batches of extracts to meet the content limits under an acceptable URE. Yan and Qu (2013) indicated that URE is affected by the correlation between the contents of components. In practice, URE decreases with the increase in the number of targets and the relative standard deviations of the contents. URE could be increased by increasing the number of storage tanks. Thus, to achieve an acceptable URE, it is desirable to use up some batches of extracts in one mixing to reduce the number of residual batches. These findings provide reference standards for designing the batch mixing process.

**Batch Mixing Optimization Model** – Yan and Qu (2013) proposed a batch mixing optimization model to reduce variation in raw materials and improve quality of the TCM under development. Their method is briefly described below.
Suppose that there are $t$ (target) components

with controlled contents in the mixture. Let *s* be the number of storage tanks, i.e., the maximum number of batches of extracts that can be stored. Also let *x*=(*x*1, *x*2, …, *xs*) be the amounts of each stored batch of extract used for mixing and *u*=(*u*1, *u*2, ⋯, *us*), the amounts of each batch of extract stored. Define *ak*=(*a*1k, *a*2k, …, *atk*)', the contents of the constituents in the *k*th batch of extract stored. For unidentified constituents, test values such as peak areas on the chromatographic fingerprint obtained by certain analytical methods can be used. Thus, we have *A*=(*a*1, *a*2, …, *as*), a *t*×*s* matrix that consists of the contents of the components in the batches of extracts stored. Now, let *b* be the amount of mixture needed in each batch and (Li, Ui) be the minimum and maximum content limits of the *i*th component. Yan and Qu (2013) proposed to maximize

max∑2=1, which maximizes the sum of squares of the used amounts of each batch under the constraints ∑=1= which determines the amount of mixture needed for the follow-up process. This optimization model can be solved by quadratic programming (QP) algorithm. In TCM manufacturing, batch mixing can be conducted with the extracts obtained from previous processes like decoction, concentration, and purification. The extracts created are first stored in the storage tanks. Batch mixing ratios are calculated according to the optimization model and mixtures are created for the follow-up process.

**Remarks** – The batch mixing process can significantly reduce the variation in the quality of TCM extracts among different batches by mixing them in a well-designed URE. The batch mixing method proposed in this work uses a minimum number of batches of extracts to meet the content limits, which is more practical in industrial production. The impacts of the important factors on URE were studied by simulations, which provide a reference for designing the batch mixing process. The results of the study have demonstrated that batch mixing is a valuable method to improve the batch-to-batch quality consistency of TCM and may contribute to the increase in consistency of the efficacy of TCM.

### 4.2 Component-to-Component Interactions

Unlike most Western medicines, TCM often consists of a number of components whose pharmacological activities may or may not be quantitatively characterized. Besides, the relative proportions (ratios) of the components for achieving optimal therapeutic effect are also unknown in addition to possible component-to-component (drug-to-drug) interaction among these components. Thus, the study of determining the relative ratios of components for achieving optimal therapeutic effect has become the key to the success of the TCM development. To study the main effects and interactions of these components, some commonly employed designs are briefly described below.

**Factorial design** – A full factorial design is a design that consists of all possible different combinations of one level from each factor. If there are levels for the h factor , the corresponding full factorial design is called a general … factorial design. For example, when =2 (or 3) for all the general factorial design is called a 2(or 3 factorial design. A 2(or 3 factorial design denotes a full factorial design at two levels (or at three levels). In practice, a factorial design is expressed in terms of a number of arrays (or runs) that indicate the levels of each factor. For example, for a typical 24 factorial design, the arrangement of the arrays is given in the following standard order (see Table 2). The first column of the design matrix consists of successive minus (−) and plus (+) signs, the second column of successive pairs of (−) and (+) signs, the third column of four (−) signs followed by four (+) signs, and so on. In general, the h column consists of 21 (−) signs followed by 21 (+) signs. In this 24 factorial design, there are four factors at two levels, with a total of 24=16 runs. The two levels of each factor are conventionally denoted by (+) and (−) (they are sometimes denoted by 1 and -1). If a variable is continuous, the two levels, (+) and (−), denoted the high and low levels. If a variable is qualitative, the two levels may denote two different types or the presence and absence of the variable. Each row represents a different combination of one level from each factor. A full factorial design provides estimates not only for main effects but also for

interactions with maximum precision. The main effects and interaction effects can easily

be obtained using a table of contrast coefficients

and/or Yate's algorithm (see, e.g., Myers,

1976; Hicks, 1982).

**Fractional factorial design** – A fractional factorial design is a design that consists of s fraction of a full factorial experiment. For example, a (12)fraction of a 2factorial design is called a 2fractional factorial design. When 1, a full factorial design reduces to a one-half factorial design. For a full 24 factorial design, there are 16 effects, including grand average, four main effects, six two-factor interactions, four three-factor interactions, and a single four-factor interaction. The full 24 factorial design contains 16 observations, which provide independent estimates for each of these 16 effects. However, if we consider only a one-half fraction (i.e., only eight observations available), due to limited resources available, it is impossible to obtain 16 independent estimates. For a 24−1 fractional factorial design, the eight observations cannot provide independent estimates for the 16 effects alone but for some confounding effects, such as the sum of a main effect and a three-factor interaction that are confounded with each other. In practice, however, the three-factor or higher-factor interactions are usually negligible (see Table 2). In this case, a fractional factorial design is useful in estimating the main effects. In practice, a fractional factorial design is useful when there are many factors to be studied because it is almost impossible to perform a full factorial design even at two levels.

**Central composite design** – A central composite design is a full factorial design or a fractional factorial design augmented by a ±level at each of the factors and central points. The central composite design consists of one center point, eight points on the cube (a 23 factorial arrangement), and six star points. It should be noted that a central composite design with 2, 1, and 1 reduces to a 32 factorial design (see Table 3). For a full 2factorial design, although the design provides independent estimates for the 21 effects, it does not give an estimate of the experimental error unless some runs are repeated. Unlike the full 2factorial design, the central composite design provides an estimate of the experimental error. The experimental error is usually estimated based on n observations at the central point.

**Remarks** – In addition to the factorial design, the fractional factorial design, and the central composite design, other designs such as the classical Plackett and Burman design (Plackett and Burman, 1946) and the factorial or fractional factorial in randomized block design are also useful.

### 4.3 Animal Studies

As indicated earlier, the use of TCM in treating critical and life-threatening diseases has had a long and noble history. It has been actively practiced nowadays in many parts of the world. Since TCM often consists of multiple components, it is unquestionable that many components are successful in suppressing different types of diseases in humans. However there does not appear to be any evidence (e.g., scientific documentations), which meets stringent Western criteria for safely and efficacy, to support their use in humans. Thus, in the pharmaceutical development, animal studies such as mice, rats, rabbits, dogs, or

monkeys for testing toxicity and evaluation of efficacy are required for regulatory review and approval before they can be used in humans.

However, there are tremendous debates regarding whether animal studies are necessary for the development of TCM, especially for those have been used in for thousands of years. Most Chinese doctors suggest that it would be better to focus on clinical development, instead of going back to animal studies to obtain evidence for a precise pharmacological profile. It would be better to focus on safety and efficacy by starting with clinical trials. It is also suggested that studies on mechanisms and active ingredients should be conducted after safety and efficacy have been confirmed.

For development of Western medicines, animal studies (models) are often used to screen experimental drugs before they enter human trials. This is animal models can provide pharmaceutical scientists the insight how do the drugs work in the living system and evaluate the toxicity at various doses assuming that animal model is predictive of human model. Although there have been controversial debates over which diseased animal models should

**Table 2. $2^{4-1}$ Fractional Factorial Design**

| | Design matrix | | | | |
|---|---|---|---|---|---|
| Run | $X_1$ | $X_2$ | $X_3$ | $X_4 = X_1X_2X_3$ | $Y$ |
| 1 | − | − | − | − | $Y_1$ |
| 2 | + | − | − | + | $Y_2$ |
| 3 | − | + | − | + | $Y_3$ |
| 4 | + | + | − | − | $Y_4$ |
| 5 | − | − | + | + | $Y_5$ |
| 6 | + | − | + | − | $Y_6$ |
| 7 | − | + | + | − | $Y_7$ |
| 8 | + | + | + | + | $Y_8$ |

**Table 3. Central Composite Design for $K = 3$ and $n = 1$**

| Run | $X_1$ | $X_2$ | $X_3$ |
|---|---|---|---|
| 1 | −1 | −1 | −1 |
| 2 | 1 | −1 | −1 |
| 3 | −1 | 1 | −1 |
| 4 | 1 | 1 | −1 |
| 5 | −1 | −1 | 1 |
| 6 | 1 | −1 | 1 |
| 7 | −1 | 1 | 1 |
| 8 | 1 | 1 | 1 |
| 9 | 0 | 0 | 0 |
| 10 | $\alpha$ | 0 | 0 |
| 11 | $-\alpha$ | 0 | 0 |
| 12 | 0 | $\alpha$ | 0 |
| 13 | 0 | $-\alpha$ | 0 |
| 14 | 0 | 0 | $\alpha$ |
| 15 | 0 | 0 | $-\alpha$ |

be used to screen new drugs before they can proceed to the clinical trials, there are certain animal models in different therapeutic areas remain good standards for drug screening used in the pharmaceutical industry, for example, the subcutaneous, xenografts in cancer drug screening, Although animal models used in the pre-clinical test do provide valuable information (if they are predictive of human models), one of the concerns is that apparent physiological and genetic differences between human and animals, which clearly indicate that the diseased models are different from the human equivalent.

### 4.4 Matching Placebo in Clinical Trials

In recent years, randomized controlled trials (RCT) have been recognized as the gold standard in clinical trials for evaluation of safety and efficacy of a test compound under investigation. One of the important components in RCTs is blinding. The ultimate goal of clinical trials is to achieve a double-blind design to avoid any possible operational biases due to the knowledge of the treatment assignment. Qi et al. (2008) conducted a comprehensive review on the validity of matching placebo used in blinded clinical trials for Chinese herbal medicine in recent years and related patents. The review was conducted based on a database called the *Wanfang Database*, which contains a total of 827 Chinese journals of medicine and/or pharmacy, from 1999 to 2005 and 598 full-length articles related to clinical trials utilizing matching placebo. A total of 77 blinded clinical trials utilizing matching placebo for Chinese medicine were extracted manually from the 598 articles. After reviewing the 77 full-length articles, it was found that nearly half of the clinical trials did not pay attention to the physical quality of the testing drug and matching placebo and whether they were comparable in terms of physical quality. The rest provided very limited information regarding the preparation of matching placebo. Thus, the integrity of blinding is questionable. Among the 598 articles, unfortunately, only 2 articles (2.6%) specifically validated the comparability between the test drug and the matching placebo. Based on this review, Qi et al. (2008) concluded that researchers in Chinese medicine commonly ignored the quality of the matching placebo in comparison to the test drug. This may have led to substantial bias in clinical trials. As a result, Qi et al. (2008) urged that quality specifications and evaluation of the matching placebo must be developed and carefully evaluated in order to reduce possible bias in randomized controlled TCM trials. As indicated by Qi et al. (2008), only a small number of randomized controlled trials in traditional Chinese medicine have been reported, most of them are of poor quality in methodology including placebo preparation and verification. Fai et al. (2011) also pointed out that in many clinical trials of Chinese herbal medicines, it is very difficult to make a quality matching placebo to achieve the purpose of blinding. Ideally, the characteristics of the test drug and matching placebo should be identical in color, appearance, smell and taste. The quality matching placebo should be identical to the test drug in physical form, sensory perception, packaging, and labeling, and it should have no pharmaceutical activity. For this purpose, Fai et al. (2011) developed a placebo capsule to match a herbal medicine in terms of its physical form, chemical nature, appearance, packaging and labeling. Based on the assessment results, the developed placebo capsule assessment results suggested that the placebo was found satisfactory in these aspects. Thus, Fai et al. (2011) concluded that a matching placebo could be created for a RCT involving herbal medicine. In addition, Fai et al. (2011) also discussed the means to acquire patent for a developed matching placebo.

It should be noted that the preparation of matching placebo is extremely important to maintain the integrity of blinding for avoid any possible operational biases that may be introduced due to the knowledge of the treatment assignment. The oral dosage form of capsule is often considered for preparation of matching placebo for clinical trials involving Chinese herbal medicines as it may remove the strong smell and taste of the herbal medicines. However, one of the major challenges is that patients or clinicians will reveal the treatment assignments if they break the capsules. Thus, standard operating procedures (SOP) for preventing patients and clinicians from breaking the capsules are necessary developed.

### 4.5 Calibration of Study Endpoints

Unlike WMs, the primary study endpoints for assessment of safety and effectiveness of a

TCM are usually assessed by a quantitative instrument or the four diagnostic procedures by experienced Chinese doctors. The assessment by a quantitative instrument has been criticized in many ways. First, it may not capture the true health of status of the patients with diseases under study (e.g., by asking wrong questions). Second, it may not detect the effect of the test treatment under investigation. As an example, consider a quantitative instrument with possible scores from 0 (perfect health) to 100 (worst possible disease status). Suppose the scores can be classified into the following categories of health status: *Health* (0-25), *Mild* (26-50), *Moderate* (51-75), and *Severe* (76-100). In this case, there is significant difference between a patient with a score of 25 (*Health*) and a patient with a score of 26 (*Mild*) despite they only differ by one point. On the other hand, a patient with a score of 26 and a patient with a score of 50 are both considered having *Mild* disease status although they differ by 24 points. Thus, the assessment based on a quantitative instrument by experienced Chinese doctors is not only subjective, but also lack of validity. Consequently, the reliability of the assessment is a concern, especially when there is evidence of large rater-to-rater variability. Thus, although the quantitative instrument is developed by the community of Chinese doctors and is considered a gold standard for assessment of safety and effectiveness of the TCM under investigation, it may not be accepted by the Western clinicians not only due to the lack of validity and reliability, but also the interpretation of the assessment (or translation of assessment to well-established and widely accepted clinical endpoints). In practice, it is very difficult for a Western clinician to conceptually understand the clinical meaning of the difference detected by the subjective Chinese quantitative instrument due to fundamental differences in medical theory, perception and practice.

Thus, for modernization or Westernization of TCMs, whether the subjective quantitative instrument can accurately and reliably assess the safety and effectiveness of the TCM is a concern for development of TCM. In practice, it is then suggested that a clinical trial be conducted to calibrate the subjective quantitative assessment against either life events or well-established clinical endpoints that are commonly used in assessment of Western medicines. The clinical trials should consist of two arms: one arm will include subjects with diseases under study diagnosed by the subjective quantitative instrument and the other arm will include subjects diagnosed by Western diagnostic or testing procedures. Each subject post-treatment will be assessed by both Chinese doctors using the quantitative instrument and Western clinicians based on the well-established and widely accepted study endpoints (Hsiao et al., 2009).

### 4.6 Package Insert

One of questions that are commonly asked in the development of a TCM is that the developed TCM is intended for use by Chinese doctors only, Western doctors, or both. The answer to this question has an impact on the preparation of package insert. As discussed in the previous section, the translation between Chinese study endpoints and Western study endpoints is not clear. As a result, it is difficult to conceptually determine the observed treatment effect (based on Chinese study endpoints) is of clinically relevance or importance.

If the TCM is intended for use by Western doctors, it must be developed under the review and approval pathway of Western medicines such as the pathway of IND/NDA of US FDA. On the other hand, if the TCM is intended for use by Chinese doctors, it will be developed under the review and approval pathway of TCMs such as regulatory requirements set forth by TFDA (Taiwan Food and Drug Administration) or CFDA (China Food and Drug Administration). In this case, the preparation of package insert is very different from that of Western medicines. If the TCM is intended for use by both Chinese doctors and Western doctors, then the calibration between Chinese study endpoints and Western study endpoints discussed in the previous section is essential.

One of the most controversial issues in development of TCMs is that the pharmaceutical development of a TCM which has been available in the market place as a lawful dietary supplement. As it is well recognized, the TCM will become a prescription drug once it is approved by the regulatory agency. In other words, the

**Table 4. Checklist of Signs and Symptoms for Psoriasis**

| Domain | Signs and Symptoms |
|---|---|
| Skin Lesion color | Full red, red, garnet, pink, darker skinned |
| Type of skin lesion | Papule, scaling, crust, pustule, cracking, erythema |
| Shape of skin lesion | Scattered, guttate, ostaceous, plaque, map, shape, generalized lesion, annular, thickness, hyperpigmentation, depigmentation, rough surface, infiltration, thin scale, thick scale, easy scaly exfoliation, dry scale |
| Associate factors | *Trigger factors*: overexertion, depression, stirring<br>*Aggravating factors*: smoking, drinking alcohol, hot water, stimulating medicine, infection, during menstruation, postpartum<br>*Predilection diet*: heavy and greasy, pungent, cold and raw<br>*Stool*: less stool, constipation<br>*Mental irritation*: sense of distress in the chest, anxiety and irritability<br>*Itching degree*: severe, mild, slight, absent<br>*Itching frequency*: continuous, intermittent<br>*Fever*: fever, hot palms, soles and heart<br>*Urine*: scanty dark urine<br>*Muscle and joint*: muscles and joint pain, stiffness with bending limitation<br>*Mouth*: dry mouth and thirsty, dry mouth and niot thirsty, bitter taste, fetid breath, sticky taste<br>*Sleep*: insomnia, frequent dreams<br>*Complexion*: flushed<br>*Nail manifestation*: nails not lustrous<br>*Menstruation*: scanty menstruation, crimson color, blood clot<br>*Throat*: sore throat, redness of pharyngeal portion, tonsil suppuration |
| Tongue and its coating | *Substance*: pale, red, maroon, dark purple tongue or tongue with petechiae, thin delicate, enlarged tongue fissured<br>*Coating*: white, yellow, greasy, glossy, rough, less, peeling, sublingual varicose veins and bluish purple |
| Pulse | Moderate, slippery, rapid, string, deep, thread, hesitant |
| Living environment | Humid, dry, hot, cold |

Source: Modified from Yang et al. (2013). *Chinese Medicine*, 8, 10. Table 2.

TCM (in the form of dietary supplement) needs to be withdrawn from the market place. This may have created problem for those subjects who have been used the TCM as dietary supplement for years.

### 4.7 Bridging Traditional Chinese Medicine

As indicated by Wang et al. (2005), the introduction of the concept of systems biology, enabling the study of living systems from a holistic perspective based on the profiling of a multitude of biochemical components. It opens up a unique and novel opportunity to reinvestigate natural products. In the study of their bioactivity, the necessary reductionistic approach on single active components has been successful in the discovery of new medicines, but at the same time the synergetic effects of components were lost.

Systems biology, and especially metabolomics, is the ultimate phenol-typing. It opens up the possibility of studying the effect of complex mixtures, such as those used in TCM, in complex biological systems; abridging it with molecular pharmacology. This approach is considered to have the potential to revolutionize natural product research and to advance
the development of scientific based herbal medicine.

## 5. Concluding Remarks

**Westernization versus Modernization** – TCM development includes the concepts of *Westernization* and *modernization*. Westernization of TCM follow current regulatory requirements at critical stages of the process for pharmaceutical/clinical development regardless there are some fundamental differences between WMs and TCMs. Modernization of TCM, on the other hand, is to develop regulatory guidance for effective evaluation of clinical safety and effectiveness of a TCM under investigation scientifically by taking the fundamental differences into consideration. Thus, one of the key issues in TCM development is to determine which approach (i.e., Westernization or modernization) is considered more feasible depending upon the nature of TCM. In practice, it is suggested that Wester clinical trials should be conducted in order to determine whether the TCM under investigation is really working regardless which approach is selected. It should be noted that for Westernization of TCM, there are similar but different regulatory requirements across different countries/regions such as European community (e.g., United Kingdom, Germany, France, and etc.), United States of America (e.g., US, Canada, and etc.)), and Asian Pacific region (e.g., Taiwan, China, Japan, South, Korea, and etc.).

**Harmonization of Regulatory Requirements** – In 2004, FDA published draft guidance on botanical drug product. In this guidance, FDA provides similar but different review and approval process for regulatory submission of TCM as compared to those of Taiwan and China (MOPH, 1992; DOH, 2004a,b). The 2004 FDA draft guidance is a milestone for modernization of TCM development. Due to fundamental differences between WMs and TCMs, practical (controversial) issues in the process of evaluation, review, and approval evitably occurred. Some of these issues are related to statistical methods for assessment of
(1) quality and consistency of raw, in-process, and end-product, (2 analytical method development and validation for quantitatively assessment of individual components, (3) the establishment of reference standards or specifications for individual components, (4) validation and QA/QC of a manufacturing process for TCM, (5) stability testing for determination of drug shelf-life, and (6) issues (e.g., preparation of matching placebo, calibration of study endpoint, and interpretation of results) in conduct of randomized controlled clinical trials. Many of these issues remain unsolved. More methodology research are needed in order to address these issues. Thus, it is suggested that these similar but different regulatory requirements be harmonized in order not only to avoid possible duplicated effort, but also to provide a more sensible way for evaluation of the TCM under investigation.

**Personalized/Individualized Medicine** – TCM could be useful alternative medicines to WMs, especially for treating critical and/or life-threatening diseases such as cardiovascular, diabetes, and cancer. The development of promising TCMs will benefit patients by providing an alternative option for treatment and hopefully for cure. The development of promising TCMs

will also enhance the search for personalized medicine since it focuses the minimization of intra-subject variability for achieving the optimal therapeutic effect. The development of new treatments (focusing on efficacy) in conjunction with TCMs (focusing the reduction of toxicity) has been the direction of future clinical research for treating critical or life-threatening diseases of many pharmaceutical companies and clinical research organizations.

**Recent Development** – As indicated earlier, Chinese doctors believe that all of the organs within a healthy subject should reach the so-called global dynamic balance or harmony among organs to maintain healthy. Once the global balance is broken at certain sites such as heart, liver or kidney, some signs and symptoms will then appear to reflect the imbalance at these sites. An experienced Chinese doctor usually assess the causes of global imbalance before a TCM with flexible doses is prescribed to fix the problem. This approach is sometimes referred to as a personalized (or individualized) medicine approach. In practice, TCM consider inspection, auscultation and olfaction, interrogation, and pulse taking and palpation as the primary diagnostic procedure. The scientific validity of these subjective and experience-based diagnostic procedures have been criticized due to (1) lack of reference standards and (2) anticipated large doctor-to-doctor variability. Cheng and Chow (2015) proposed a unified approach for developing a composite health index for diagnosis of illness based on a number of indices collected from a given subject under the concept of global dynamic balance among organs. Dynamic balance among organs can be defined as follows. Following the concept of testing bioequivalence or biosimilarity, if the 95% confidence of a given index is totally within some balance limits, e.g., (□ □□ □), we conclude that there is dynamic balance among organs of the subject. If we fail to reject the null hypothesis, we conclude that there is a signal of illness. In practice, these signals of illness can be grouped to diagnose specific diseases based on some pre-specified reference standards for diseases status of specific diseases which are developed based on indices related to specific organs (or diseases)

**Future Perspectives** – In practice, it is recognized that WMs tend to achieve the therapeutic effect sooner than that of TCMs for critical and/or life-threatening diseases. TCMs are found to be useful for patients with chronic diseases or non-life-threatening diseases. In many cases, TCMs have shown to be effective in reducing toxicities or improving safety profile for patients with critical and/or life-threatening diseases. As a strategy for TCM research and development, it is suggested that (1) TCM be used in conjunction with a well-established WM as a supplement to improve its safety profile and/or enhance therapeutic effect whenever possible, and (2) TCM should be considered as the second line or third line treatment for patients who fail to respond to the available treatments. However, some sponsors are interested in focusing on the development of TCM as a dietary supplement due to (1) the lack or ambiguity of regulatory requirements, (2) the lack of understanding of the medical theory/mechanism of TCM, (3) the confidentiality of non-disclosure of the multiple components, and (4) the lack of understanding of pharmacological activities of the multiple components of TCM. Since TCM consists of multiple components which may be manufactured from different sites or locations, the post-approval consistency in quality of the final product is both a challenge to the sponsor and a concern to the regulatory authority. As a result, some post-approval tests, such as tests for content uniformity, weight variation, and/or dissolution and (manufacturing) process validation, must be performed for quality assurance before the approved TCM can be released for use.

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