

## Application of quality control principles to herbal drugs

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### Abstract

Quality is conformance to requirement and meeting stated as well as implied needs of customer. The word quality is derived from Latin '*qualis*' means 'of what kind' and encompasses composition and properties of object. Quality is of paramount importance when it is specifically related with drugs. And when it comes to herbal drugs, because of several reasons is a herculean task. The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. The setting of global standards is requested in Article 2 of the WHO Constitution, which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". The World Health Assembly - in resolutions WHA31.33 (1978), WHA40.33 (1987) and WHA42.43 (1989) - has emphasized the need to ensure the quality of medicinal plant products by using modern control techniques and applying suitable standards. This manual describes a series of tests for assessing the quality of medicinal plant materials. The tests are designed primarily for use in national drug quality control laboratories in developing countries, and complement those described in 'The international pharmacopoeia' which provides quality specifications only for the few plant materials that are included in the WHO 'Model List of Essential Drugs'. In this review, we have addressed some important issues related to quality of botanicals and discussed possible application of total quality management for herbal drugs.

**Keywords:** WHO, Herbal Drugs, Quality Control.

### Introduction

Quality control is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. New and better medicinal agents are being produced at an accelerated rate. At the same time more exacting and

sophisticated analytical methods are being developed for their evaluation [1].

Before application of newer tools of quality control, it is necessary to get insight of herbal drugs. WHO defines traditional medicine as including diverse health practices, approaches, knowledge and beliefs incorporating plant, animal and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to

maintain well-being, as well as to treat, diagnose or prevent illness. Natural products include various plants, animals as well as minerals. Plants serve as most valuable source for curing many diseases. Herbal medicines include herbal extracts, herbal drug preparations and herbal drugs. Herbal drugs are unprocessed part of plant or whole plant. Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered. Herbal preparations include comminuted or powdered materials or extracts, tinctures and fatty oils of herbal materials, which may be produced by extraction, fractionation, purification, concentration or other physical or biological processes. Herbal medicines are used very commonly in various health practices or therapies of Traditional Medicines like Chinese medicine, Ayurveda, Unani, Naturopathy, Osteopathy and Homeopathy. As herbal wave sweeping over society is rising, many of the major pharmaceutical companies have renewed their strategies in favor of herbal drugs so the time seems to ripe for botanicals of better quality [2].

### **WHO Guidelines for Quality Standardized Herbal formulations**

Standardization and quality control parameters for herbal formulations are based on following fundamental parameters:

1. Quality control of crude drugs material, plant preparations and finished products.
2. Stability assessment and shelf life.
3. Safety assessment; documentation of safety based on experience or toxicological studies.
4. Assessment of efficacy by ethnomedical information and biological activity evaluations.

### **Quality Control of Crude Material**

According to pharmaceutical manufacturers association of U.S. "quality is the sum of all the factors which contribute directly or indirectly to the safety, effectiveness and acceptability of the product"[3]. Standardization describes all measures taken during manufacturing process and quality control leads to reproducible quality of particular product. Growing need for standardization and quality control of herbal medicines is recognized by WHO. In policies and checklist on Traditional Medicine(TM) WHO has given emphasis on development of national standards

and technical guidelines and methodology for evaluating safety, efficacy and quality of TM. As well as WHO also gives stress on development of national pharmacopoeia and monographs of medicinal plants, cultivation and conservation of medicinal plants to ensure their sustainable use are also prime importance as botanicals are considered [4]. Standardization of botanicals offers many obstacles because synthetic drugs have well defined structure and other analytical parameters as well as reference standard for comparison also established assays and pharmacopoeias. Therefore, quality control is not problematic for synthetic drug [5]. There are several challenges as standardization of herbal product is considered like controversial identity of various plants, deliberated adulteration of plant material, problems in storage and transport, which should be considered [6].

One of the impediments in the acceptance of the herbal products worldwide is the lack of standard quality control profiles. Most of the herbal formulations, especially the classical formulations of traditional medicine, are polyherbal. Each formulation contains 10-20 or more ingredients; a few have even 50-75 ingredients. Many preparations are either liquid or semisolid. For such formulations it is very difficult to establish parameters for quality control. Even official standards are not available. The unique processing methods followed for the manufacture of these drugs turn the single drugs into very complex mixture, from which separation, identification and analysis of the components is a very difficult.

In Germany, physicians are required to have some training in herbal medicine. Considerable research on herbal medicine including double-blind, placebo-controlled trials are ongoing. Physicians recommend and patients use herbal medicines extensively. Manufacturers are required to meet standards of purity and pharmaceutical activity. Commission E, which has had oversight of herbal medicines and has determined their safety and efficacy, has published 387 monographs (recently translated into English by the American Botanical Council). Several other European countries also have policies and procedures that allow rational oversight of herbal medicines [7].

In the United States, herbs are used either as dietary supplements, with minimal standards of safety and efficacy, or as drugs, which require expensive and cumbersome testing procedures. Middle-of-the-road

approach that acknowledges the long history of use of many herbal medicines, examines data from many sources including other countries, insists on strict production standards, and requires absolute safety and a classification of efficacy that may vary from "unproved" for some conditions to "demonstrated" for others. The use of the translated Commission E monographs would be very helpful for patients and physicians.

### Identity of Plant Material

Authenticity, purity and assay are important aspects of the standardization and quality control. As the name implies authenticity relates to proving the material is true and corresponds to right identity. Quality control of botanicals starts right from identification of plant. According to WHO general guidelines for methodologies on research and evaluation of traditional medicines, first step in assuring quality, safety, and efficacy of traditional medicines is correct identification. As plant can be named in four different ways, the common English name, the transliterated name, the Latinized pharmaceutical name, the scientific name. When binomial names are not used misidentification can occur. For example, the scientific name of the Chinese herb that is variously transliterated as "dong quai", "dong guai", and "tang kuei" is *Angelica polymorpha* (formerly *sinensis*). The common English name "Angelica" and Latinized name "*Radix angelica*" could refer either to this species, which is used in Australia, or to the Europe species *Angelica archangelica*, depending upon the country of the origin [8].

Many times two or more different plants have same name in Ayurveda. Ayurveda use plants by Sanskrit names and there are instances where the same name stands for two or three different plants. So, in spite of botanical identification, there is still confusion with respect to some Ayurvedic drugs. *Boerhaavia diffusa* widely used as 'quality of life enhancer' and the plant *Trianthema portulacastrum* both, for instance, are known as "Punarva" and both plants may be used at same time. Another well-known example is of *Sankhapushpi*, an important *medhya* drug used for improvement of memory power and intellect. *Shankhapushpi* is equated with one or other of the following plants depending on the region in India: *Canscora decussata*, *Evolvulus alsinoides* and *Clitoria*

*ternataand* and sometimes *Convulvularis pluricalis*. There seems to be a lot of confusion in correlating the terms *Vishnukranti*, *Shankhapuspi*, *Aparajita*, *Girikarni* etc. to the respective botanical sources. All local trade occurs by these vernacular names add to confusion. Another problem for Ayurvedic drugs is that, there are 56 standard books and different manufactures use different reference book, which obviously bring about manufacture to manufacture variation in same product.

Misunderstanding problems in procurement of authentic plant materials are due to:

1. Collection of wildy growing plants from forests and wastelands.
2. Traders or suppliers generally have limited knowledge of medicinal plants
3. Folk populace and laborers who are not fully aware of the identity of the drugs always do collections.
4. Non homogeneity of plant material due to collection from wild sources and different geographical locations [9].

Chemical analysis is so far best method for standardization and to detect contamination and for plant identification and authentication of medicinal plants. Molecular biology techniques can also applied to authentication of medicinal plants as complimentary techniques [10].

### Variations in Botanicals

Consistency in composition and biologic activity are essential requirements for the safe and effective use of therapeutic agents. However, botanical preparations rarely meet this standard, as a result of problems in identifying plants, genetic variability, variable growing conditions, differences in harvesting procedures and processing of extracts, and above all, the lack of information about active pharmacologic principles [11]. Environmental conditions such as sunlight, rainfall, altitude, temperature, soil, storage conditions as well as different harvesting procedures, time and method of collection, manufacturing processes such as selecting, drying, purifying, extracting, and genetic variability can create substantial variability in product quality and in the concentration of plant chemicals within different products. Ecological conditions like insect feeding, microbial infections may affect secondary metabolites and in turn chemical

composition of the plant. Also different parts of same plant (example roots, stem and leaves) contain different concentration of chemical constituents. At the same time diurnal variations (for example paclitaxel, opium alkaloids) and seasonal changes also account for variability in herbal medicines. The therapeutic or toxic components of plant vary depending on the part of the plant used as well as stages of ripeness [12]. Products from different manufacture vary considerably and it is not possible to control all the factors that affect the plants chemical composition [13]. Consistency in composition and biological activity is essential requirement for the safe and effective use of therapeutic agent. As botanicals are prone to contamination, deterioration there may be batch to batch variation in composition. Each herb contains large number of diverse compounds and it is not possible to analyze for presence or absence for all compounds. Modern chromatographic techniques use chemical markers, which may not be therapeutically active. For many herbs the active constituents are not known in this case product may be standardized on content of certain marker compounds which are chemical characteristic of herb or present in large amount. Another well-known example of new active marker is St John's wort. In St John's wort previously it was thought that active constituent is hyperforin but later come to know, hypericin has that antidepressant activity. So these approaches make assumptions that about the relation between the quantity of marker and that of the unknown active constituent [14].

### **Safety Assessment; Documentation of Safety Based on Experience or Toxicological studies**

Adulteration of botanical preparations is another important issue. Due to over exploitation of certain plants, habitat loss and fragmentation of the forest, many medicinal plants have reached to the level of the endangered or rare species. These and many other factors (like cost of raw material) cause problem for availability of genuine drug, which encourages the adulteration of plant by substitution with inferior commercial varieties, artificially manufactured substances, exhausted drugs or cheaper plant or by another vegetative part [15]. Several reports suggest that many herbal products contain undisclosed pharmaceuticals and heavy metals [16]. The intentional use of pharmaceutical adulterant is possible. Agrochemicals are used to protect the plant from

infections and insects, which occur as contaminant in the crude plant material. More over mechanism of action, pharmacokinetics and drug-drug interactions of many herbs are still in infancy. At the same time growing number of reports about fatal or adverse effects of herbal preparations intensifies need for national regulation and registration of herbal medicines and establishment of safety monitoring. Clinicians should not prescribe or recommend herbal remedies without well-established efficacy as if they were medications that had been proved effective by rigorous study. However, these products continue to have great appeal to patients, and this reality cannot be ignored. Thus, it is imperative to ask patients. This also signifies real need for quality control of botanicals [17].

Need of quality control and standardization of herbal product can be summarized as follows:

1. When traditional medicines were developed technology and concept of standardization was quite different.
2. During past thousand years dynamic process of evolution may have changed the identity of plant material.
3. Due to commercialization, supply of genuine raw material has become a challenge.
4. Properties of botanicals may have undergone change due to time and environmental factors [18].

These all factors adversely affect quality of crude drug and consequently, formulations manufactured by using them as ingredient [19]. After this background, it is interesting to study how newer quality related tools can be applied for herbal drugs.

The word quality is defined by various ways. It is important to understand concept of quality when dealing with quality control. According to ISO 9000, quality is "Degree to which a set of inherent characteristics fulfills requirements". The standard defines requirement as need or expectation. Six sigma defines it as "Number of defects per million opportunities". Philip B. Crosby definition quality is "Conformance to requirements". The requirements may not fully represent customer expectations; Crosby treats this as a separate problem. According to Joseph M. Juran, quality means "Fitness for use". Fitness is defined by the customer. There are some other definitions also. Robert Pirsig: "The result of care". Genichi Taguchi, comes with two definition. First one is "Uniformity around a target value". The idea is to

lower the standard deviation in outcomes, and to keep the range of outcomes to a certain number of standard deviations, with rare exceptions. Second one is "The loss a product imposes on society after it is shipped". This definition of quality is based on a more comprehensive view of the production system. American Society for Quality: "A subjective term for which each person has his or her own definition. In technical usage, quality can have two meanings: First, the characteristics of a product or service that bear on its ability to satisfy stated or implied needs and second, a product or service free of deficiencies".

### Concept of Validation

In order to control quality of herbal drugs in better way, we must amalgamate newer techniques and terms to maximum extent. USFDA defines validation as, "Validation is documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predefined specifications and quality attributes". In early days, when the concept of validation came to a pharmaceutical industry there was misinterpretation of the meaning of validation i.e. validation is nothing but wastage of time and money. But over the period of time this concept is get changed i.e. validation is not wastage of time and money but it is an investment of time and money resulting in a production of a quality product.

This concept of validation is getting well applied to manufacturing of synthetic drugs from long time back. But this concept is not that much deeply or methodically studied and applied for the manufacturing of herbal drugs. All international regulations like USFDA, MCC, MHRA, TGA etc. shows the applicability of validation to pharmaceutical manufacturing but no one regulation except WHO applies the validation concept to manufacturing of herbal drugs. WHO also emphasize on very little part of validation. Due to that reason the authors want to emphasize on the concept of validation and also the validation model for manufacturing of herbal drugs. There is simple and mostly used validation model for manufacturing of synthetic drugs.

Validation model for synthetic drugs:



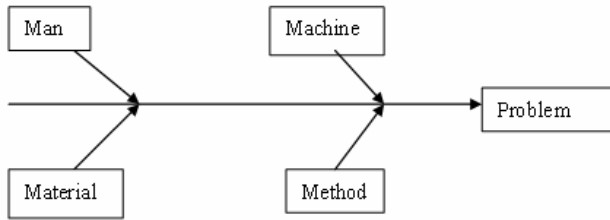
We propose how this model is applied to for manufacturing of herbal drugs and also the limitation of that validation model for synthetic drugs. Generally one can describe this model straightforward that means starting from input and ends to output. But in case of validation one has to go in reverse direction. First of all to identify and define which type of quality product required i.e. product has its own identity, strength, safety, purity and efficacy. This is explained by taking one example of herbal tablet or Gutika.

1. Identity - having specific shape, packing (strip or blister or alu-alu)
2. Strength - having specific strength (500mg/tablet, strip of 10 tablets having 500mg/tablet etc.)
3. Safety - safe for both i.e. person who is engaged in manufacturing and the person who is going to take that tablet.
4. Purity - shows purity (99.9% pure)
5. Efficacy - it shows the desired therapeutic efficacy.
6. After deciding the required output, the processes and its parameter are defined, e.g. for manufacturing of tablet (Gutika),
7. Mixing - how much time is required for mixing?
8. Granulation - which type of granulation (Wet or Dry) for how much time?
9. Compression - how much pressure and for how much of time is required?
10. Packing - which type of packing (strip or blister or alu-alu)?

And lastly that means after defining output and process, the inputs are defined. Example: for manufacturing of tablet (Gutika),

1. Personnel
2. Equipments
3. Raw material
4. Packaging material
5. Environmental conditions – temperature, pressure differential, no. of air changes/hr. etc.

This same model is applicable for herbal drugs but there are some limitations such as in case of synthetic drugs one can go up to vendor certification (Input) but in case of herbal drugs one has to go beyond that i.e. not up to vendor certification but up to manufacturers certification. The manufacturer certification is difficult process but it is possible and this is the need of the



**Fig 1: Pareto cause and effect diagram.**

today's herbal industry. One more reason to certify the manufacturer is a standardization problem particularly the strength of active moiety or drug. So that the validation model for manufacturing of synthetic drugs is get modified i.e.

**Validation Model for Manufacturing of Herbal drugs**

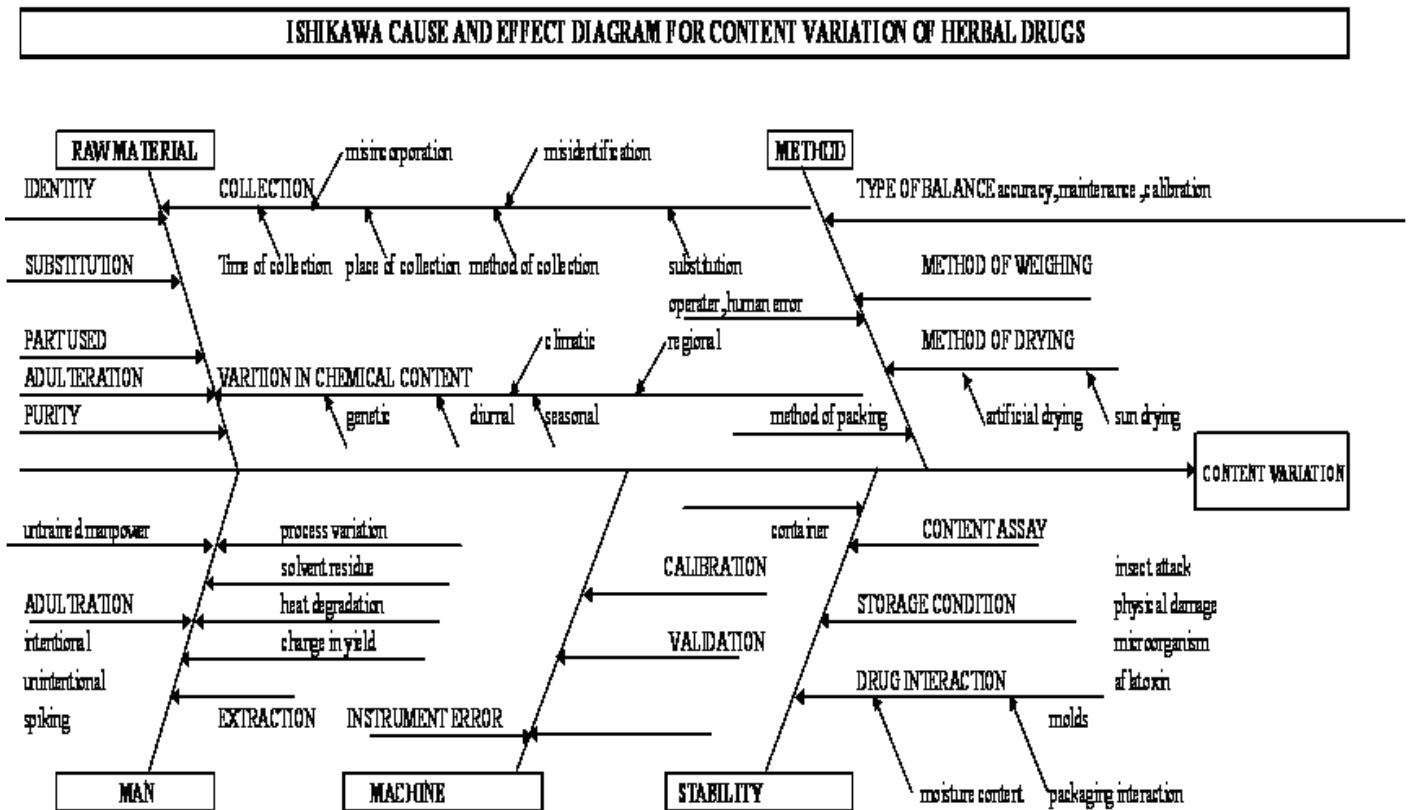
There are lots of parameters which has to be considered while certifying the manufacturer:



1. Type of Herbs
2. Environmental conditions
3. Time of collection etc.
4. Variation in composition

**Total Quality Management (TQM) rather than Quality Control:**

Let's look towards difference between TQM and QC. Quality control which is generally done at the end of operation, mainly control material and product. Growing need for quality necessitate the more comprehensive technique like Quality Assurance which focuses on material, product and process and is on line activity. But TQM is more comprehensive which covers material, product and all process and starts before beginning of operation.



**Fig 2: Ishikawa cause and effect diagram for content variation of herbal drugs.**

TQM is striving for quality which not only includes controlling but also planning, auditing and continuous improvement. There are many techniques and tools of TQM which can be viewed as key to solve critical problem of quality in herbal drugs. To discuss all techniques in detail is beyond the scope of this review, so we have discussed some of the important techniques in brief.

Pareto, an Italian economist realized that approx 90 percent of the wealth in his country was owned by 10 percent of the people [20]. According to this 'vital few and trivial many' concept can be applied for herbal drugs. The only vital problem that is control of raw material can solve many trivial problems associated with quality. At the same time application of six sigma can be possible for quality of herbal drugs. The inherent variability in herbal drugs cause the output varies over a period of time. If this variability is considerable, it is impossible to predict the value of a characteristic of any single item or at any period of time. Any defect in a component, product and service could be due to one or more causes. To find out the relationship between the cause and effect, a diagram is drawn systematically by mapping out all the probable causes influencing the effect is called as cause and effect diagram or Ishikawa diagram or fishbone diagram. The concept of Statistical Quality control (SQC) as proposed by Dr. Deming can be used effectively to address this issue. Demings PDCA (Plan, Do, Check and Act) cycle not only maintain quality but also improves when cycle goes on running [21].

Following are some examples of cause and effect diagram: This basic cause and effect diagram can be applied to detect the problems associated with herbal drugs for better quality control in following manner (Figure 1, 2)

## Conclusion

Because of gravity of the problem, profound knowledge of the important herbs found in India and widely used in Ayurvedic formulation along with new standardization techniques is of utmost importance. Incorporation of this will authenticate quality thereby reducing further problems. Quality is inspected at right starting point then it will eliminate all bottlenecks in quality control of herbal formulations to obtain better formulations. We wish to draw the attention of readers

to the rapidly evolving standardization aspects of herbal drugs with some new ideas, so that this area could be expanded significantly. More emphasis should be given on total quality management (TQM) for better quality of herbal drugs. Then one can dream a utopian situation where quality is built in the product so deeply, that there should be no need to control.

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