

REVIEW

VALIDATION METHODS AND STANDARDS FOR HERBAL MEDICINE

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General Introduction

During the last decade of the 20th century, the phytochemical, biological and clinical data accumulated, reveals that plant based herbal remedies are the emerging choice to treat many diseases and ailments. Thus herbal medicines have once again appeared and surfaced along with the scientific advances to create a growing admiration for application and technology to manufacture herbal medicaments in the form of desired pharmaceutical dosage forms. The importance of plant based medicines, therefore, has also attracted the attention of regulatory bodies controlling the food and drug administration both in the developing and developed countries throughout the world. This surge in interest in phytotherapy, alternative, complimentary or traditional medicine have equally been advanced by the World Health Organization (WHO). On the basis, that 80% of the population of an estimated 4 billion people of the world population use herbal medicine as the primary health care. The sophistication of herbal remedies utilized by the people living on the face of this earth, varies with acquisition of technologies as it is being evolved at a fast speed. Consequently, the production of phytomedicine are documented for safety, efficacy and quality. The world health agencies have already recognized the need to standardize herbal medicines and set guidelines for their production and quality assurance (WHO, 1999).

Globally, phytomedicines have been

researched under rigorous controls and have been approved by drug control agencies of the governments of technologically advanced nations. The process of scientific validation is good to excellent and the history of clinical use is even stronger. Many herbal medicines produced have been prescribed by thousands of physicians in their practice and are consumed under medical supervision by ten of millions of people. Much of the literature can be found in private, official and non-official compendia including the databases developed and maintained by different organizations and institutions. However, basic research on plant medicines and their biologically effective components in terms of standardized content and their potential toxicity is needed to be conducted to allow safe and replicable research documents of specific clinical utility.

The increased use of herbal medicine has potential for improving public health and lowering health care cost. Further, plant medicines if combined with the preventive design/model of medical practice it could also appreciably be cost-effective, and can assist practically and effectively in shifting the focus of attention of modern (allopathic) healthcare from disease treatment to that of prevention, as old saying goes "*prevention is better than cure.*" The regulatory requirement is another dimension, which in time to come has to be applied by herbal drug manufacturers, or herbal drug industry as the requirement for proof of scientific validation. The bias against plant medicine must be

eliminated by redesigning the requirements for proof of efficacy, more concentrating on safety and by allowing the scientific validation to take its roots and course to be adopted by phytomedicine industrial set up. There are already scientific validation models being applied for the production and development of allopathic medicine, these models can be adopted as guides for the herbs-based drug development and manufacture following a reasonable plan and strategy. Adopting a more realistic standard of evidence for herbal drug, documented evidence can be presented for scientific validation of safety, efficacy and quality (Farnsworth N.R. *et al.*, 1985).

Process Validation

Process validation is a documented programme which can provide a high degree of assurance that a specific process can consistently produce a product (herbal medicine) meeting its pre-determined specifications. Therefore, validation will be for establishing a documented evidence that a system does produce a herbal medicine what it purports to serve. The validation is *per se* an outcome of quality functions of activities and endeavors combined with quality control which is a regulatory process and in turn is measured with actual quality performance against the standard and acts on the difference. The process of validation can be classified into two broad areas of application such as:

- i. **Sterilization Process:** a treatment process from which probability of any microorganism survival is less than 10⁶ or one in a million.
- ii. **Non-sterilization Process:** Any treatment process which purports to do something other than to sterilize.

Generally the validation programme should establish goals and objectives as to achieve herbal medicine in which dosage form is to be validated. This in turn will involve the equipment/machines to be used for manufacturing, protocols to be adopted, acquisition of data and its evaluation, preparation of summary of the results of

production and management, and lastly the change of control procedure to ensure the compactness and completeness of validation (Parantral Drug Association, 1991; John Y. Lee 1999).

The validation measures as to the above validation programme may further be expanded such as:

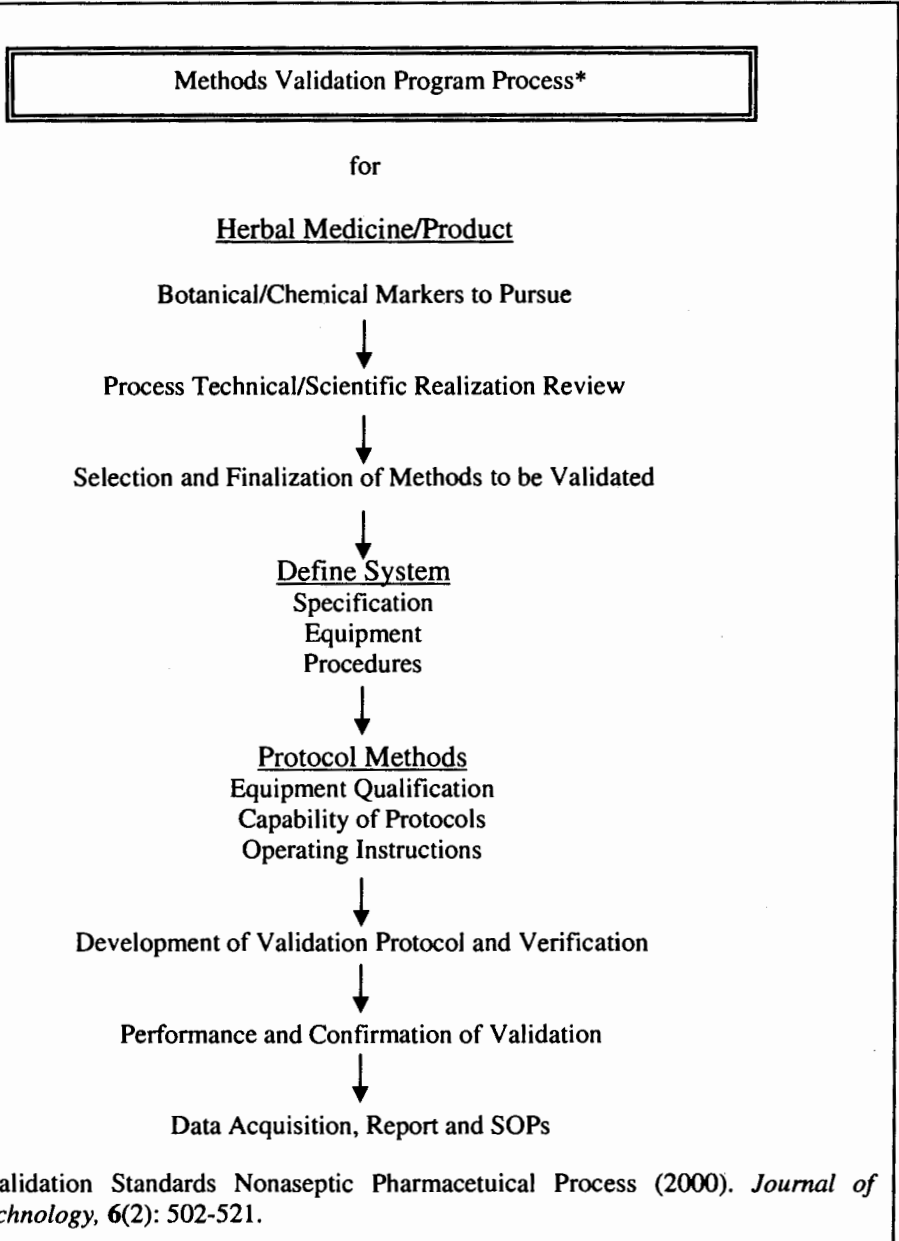
- a. Comprehensive product definition
- b. Formulation with active substance and relevant excipients
- c. Source of component material and specification
- d. Analytical test methods and controls test procedures
- e. Manufacturing process instructions
- f. Equipments/machines (automated and non-automated)
- g. Support system including standard operating procedures (SOPs)
- h. Results and records

Basically the elements of qualification for the validation, broadly speaking, may be grouped into three categories, viz.

1. Installation Qualification (IQ)
2. Operational Qualification (OQ)
3. Performance Qualification (PQ)

Installation and Operation qualifications are to be conducted and documented in a manner that ensure proper installation and functionality of all processing equipment, and permits effective change control.

1. Installation qualification includes list of all equipment, operation of which has potential bearing on product quality or process performance.
2. Operation qualification is to include identification steps, unit operation or stages of the process, as well as operating parameters.
3. Performance qualification should cover the range of process operating parameters, product specification fully defined and completed IQ and OQ step operations, operating personnel or qualified human resource to execute the validation.



Validation Standards for Herbal Medicines

While standards for manufacturing and testing of pharmaceutical products are well established, the standards for herbal medicine are still in developmental stages. However, some documents are available like *British Pharmacopoeia*, *German SE-30 Herbal*

Monograph and other non-official compendia provide standards for good manufacturing practices (GMP) and testing a score of approximately 200 herbal medicines. WHO has emphasized the need to ensure quality control of medicinal plant products by using modern techniques and applying suitable standards. The *International Pharmacopoeia*

provides quality specification for only those plant materials, which are included in WHO model list of essential drugs (WHO, 1998).

The specification for herbal medicine should indicate the powder fineness and sieve size, organoleptic analysis of sampling of material in bulk, determination of foreign matter, powdered microscopy, histological and histochemical observations, Thin layer chromatographic techniques, determination of ash value, extractable matter, water and volatile matter contents, haemolytic activity, determination of swelling index, foaming index, pesticide residue particularly arsenic and heavy metals, microorganisms and other allied parameters (WHO, 1992).

Therefore looking from the development of agri-based biological, chemical and processing technologies for the production of clinically effective herbal medicine, is to be given the top priority for self-sustenance of the economy. Basic research in the plant taxonomy, phytochemistry, phytopharmacology, phytotherapeutic evaluation and efficacy is therefore essential. Toxicology forms an important and integral part of the development of herbal medicine and phytotherapy. The basic problem is the regular and sustainable supplies through standard agriculture produce and productivity. Where in the development of agronomic application includes crop improvement for higher yield per unit of area of medicinal herbs/plants, agricultural product, pro-drug herbal produce, drying, garbling and preparation for the pharmaceutical marketing which ultimately provides ample assistance for the input of herbal pharmaceutical industry leading to the manufacture of herbal medicine. Some of the technologies so far developed (Report, CIMAP 2000), for the representative phytotherapeutic medicaments can be cited as:

- a. High yielding varieties of Japanese mint, Spearmint, Scotch Spearmint, Bergamot mint, Hill mint etc.
- b. High yielding varieties of Palmarosa,

Citronellal Java, Lemon grass, Vetiver, Lavender, Rose for essential oil and fragrance.

- c. Introduction of new varieties of Rose including Bulgarian and Persian rose.
- d. Extraction and crystallization of menthol-rich varieties of *Mentha*.
- e. Technology for the production of Rye-ergot.
- f. Pyrethrum and Neem as natural insecticides.
- g. Production of artemisinin from *Artemisia annua*, an anti-malarial herbal medicine.
- h. Colchicine from *Gloriosa superba*, an antitumor agent.
- i. Ajmalicine from *Catharanthus* root.
- j. Diosgenin from rhizomes of *Dioscorea deltoidea*.
- k. Berberine hydrochloride from *Berberis* spp.
- l. Jasmine concrete and absolute from Jasmine flowers.
- m. Tuberose concrete and absolute from tuberose flowers.
- n. Ginsenosides as secondary metabolites from *Ginseng* spp.

Above mentioned some of the examples which relate the development of improved varieties, appropriate technologies and their validation for the development of basic raw material, pro-drug molecules and in general manufacturing of herbal medicine. All this suffice to explain that developmental efforts should be expanded to adjust the necessary technical and process validation needed for the implementation of good manufacturing industrial strategy aimed at the development of herbal medicine. Further mechanism for ensuring the safety and control of herbal medicine needs to be introduced through the route of herbal validation and process. Improving research capacity and quality assurance of herbal medicine may be more conveniently achieved via the validation program support.

Similarly, part thereof the validation is the process such as to support production of

high quality botanical products. There are many organizations which cater to validate and make available analytical methods so that the need to fulfill the global consistency in testing is achieved. It is because of the facts that botanicals present with unique challenges to develop standardized methods of analysis for the herbal medicine. It is imperative that uniform analytical methods for herbal medicine should be collaborated along with the clinical support, stability testing, active ingredient analysis and manufacturing. Although there are available established laboratory techniques to analyze pharmaceuticals according to official and unofficial compendia like *USP*, *BP*, *BPC*, *International Pharmacopoeia* etc. But there are very few documented monograph available (like *British Herbal Pharmacopoeia* and *SE-30 German Herbal Monograph*) and these also present a limited number of plant based materia medica. Therefore, validation of botanicals, and their active components, methods have to be developed under the heading of *Methods of Validation Program*. The validation should be applicable to both raw material and extracts to be made into herbal medicine. It will be more appropriate to validate the methods to the inventory or primary product as medicinal herbs / plants (starting material), because the finished product application would be too complex and impractical to evaluate finished product matrixes being marketed. In this way herbal medicine producer can thrive two folds i.e. to build a consumer confidence in the efficacious quality product, as well as advancing the industry on the validation bench work for their future growth.

In order to suffice and to show the strength of Validation Method Program the following documented methods are being included as representative examples:

- i. Kavalactone in *Piper methysticum* by High Performance Liquid Chromatography (HPLC) (Fig-i).
- ii. Flavonal glucoside in *Gingko biloba* by HPLC.
- iii. Ginsenosides in Korean Ginseng and American Ginseng by HPLC.
- iv. Chromatographic constituents, identification of *Hypericum perforatum* by HPLC.
- v. Ginkgoterpenoid from *Gingko biloba* by HPLC.
- vi. Total polyphenols in *Echinacea* spp. by HPLC.
- vii. Hypericin and pseudohypericin by HPLC.
- viii. Fatty acids / Sterols contents in Saw Palmetto (*Serenoa repens*) by gas chromatography (GC).
- ix. Allicin contents in Garlic by HPLC.

A representative detailed monograph to determine Kavalactone assay by HPLC is being developed by the Institute of Naturaceutical Advancement is being reproduced here for the understanding of the validation methods in detail:

Kavalactone Assay by HPLC

Assay Title: Determination of kavalactones (α -pyrones and substituted 5,6-dihydro-cc-pyrones) in *Piper methysticum* by High Performance Liquid Chromatography.

Scope: This assay can be used to determine methysticin, dihydro-methysticin (DHM), kavain, dihydrokavain (KHK), desmethoxyyangonin, and yangonin content in kava plant material and kava soft extract (Singh Y.D., 1999 and Yu Shao K.H. et al., 1998).

Safety Precautions:

Consult the Material Safety Data Sheet (MSDS) for any chemical used that is unfamiliar. All chemicals should be considered hazardous. Avoid direct physical contact.

Principle: Plant material or extract is extracted / dissolved using methanol and analyzed by HPLC against external standards of each kavalactone. The HPLC

column is YMCbasic C8, 4.6 x 250 mm, the mobile phase is isocratic acetonitrile/water/methanol at 1.0 ml/minute and detection in U.V. at 220 nm.

Standards: Desmethoxyyangonin (Addipharma, Batch No. RDY 00197, Sales No. RDY 001 004)
 Dihydromethysticin (Addipharma, Batch No. RDM 00298, Sales No. VDM 002 002)
 Dihydrokavain (Addipharma, Batch No. RDK 00197, Sales No. VDK 001 005)
 Methysticin (Addipharnia, Batch No. RME 00197, Sales No. VME 001 003)
 Yangonin (Addipharma, Batch No. RYA 00197, Sales No. VYA 001 004)
 Kavain (Addipharma, Batch No. LHKA 00197, Sales No. VKA 001 007)

Note: This is not an all-inclusive listing of sources for reference standards. World wide there are many reputable suppliers of botanical reference standards whose products may be used. However quality control protocol and/or government regulation may mandate further qualification of the materials for proper identity and purity.

Standard Preparation

Prepare a mixed stock standard by accurately weighing (± 0.01 mg) about 10 mg of each kavalactone reference standard into a 10-mL volumetric flask. Add 7.0 ml of methanol and sonicate until dissolved. Dilute to volume with methanol and mix.

Note: Alternatively, prepare a kavain stock standard in a like manner and use the kavalactone

response factors to quantify against.

Dilute the stock standard to create a minimum of a four-point standard curve. Suggested standard dilutions of the stock are 1:10, 1:25, and 1:100 using methanol.

Notice: Store standards at refrigerated temperatures (0-5°C). **Kavalactones degrade rapidly after 48 hours.** Preparation of fresh reference standards before each analysis is recommended.

Apparatus: Calibrated analytical balance accurate to ± 0.01 mg.

Flask, volumetric, Class A, assorted size Vials, chromatography with cap.

High Performance Liquid Chromatography System, Hewlett Packard Model 1050 or 1100 equipped with an autosampler, U.V.-VIS detection, and HP-ChemStation computer, orequivalent Filter, 0.45 μ m, Gelman Acrodisc® nylon (P/N 4426), Whatman Puradisc™ Polypropylene (Cat. No.6788-2504), Whatman GD/X Glass (Cat. No. 6894-2504) or equivalent.

Sonicator.

Column, YMC basic C8, 5 mm, 4.6 x 250 mm (Cat. No.BA99S05-2546WT).

Reagents Water, HPLC grade or Nanopure
 Methanol, HPLC grade
 Acetonitrile, HPLC grade
 Acetic Acid, glacial, ACS Reagent grade

Sample Preparation

Plant Material

Accurately weigh (± 0.1 mg) about 750 mg of finely ground stem, peeling, or root material.

Place the material into a 50-mL

volumetric flask along with 40 ml of methanol/water 970/30). Sonicate for 60 minutes at room temperature.

Allow flask to cool to room temperature and dilute to volume with methanol/water (70/30) and mix.

Filter and place sample into a HPLC vial and cap.

Soft Extract (Paste)

Accurately weigh (± 0.1 mg) about 100 mg of extract into a 50-mL volumetric flask. (The 100-mg weight is based upon a 50-60% kavalactone content in the extract).

Notice: **Carefully homogenize extract before sampling.** This is accomplished by placing the extract in a container immersed in a 60°-80°C hot water bath until free flowing.

Add 40 ml of methanol and sonicate for 10 minutes or until all of the solids have dissolved.

Allow flask to cool to room temperature and dilute to volume with methanol and mix.

Filter and place sample into a HPLC vial and cap.

Powder Samples

Kava extract is often blended or spray dried onto various carriers.

This method is not validated for these matrixes. To successfully assay powder samples, it is necessary to develop a sample preparation step that recovers the kavalactones from the carrier. This sometimes can be accomplished by first extracting with pure methanol or water. However, no general guidelines can be given due to the wide range of carriers used and their individual chemical and physical characteristics.

Chromatographic Conditions

Column YMCbasic C8, 5 μ m,
4.6 x 250 m

Column

Temperature 40°C

Flow Rate 1.0 ml/minute

Mobile Phase Isocratic

Acetonitrile:Methanol: Water: Acetic Acid
(20:20:60:0.1 v/v)

Detector 220 nm

Inj. Volume 5 μ L

Run Time 40 minutes

Procedure Prepare reference standard solutions and sample preparation as directed.

Make a single injection of an extraction solvent blank.

Make single injection of the standard preparations.

Create a linearity plot of standard peak areas versus standard concentrations.

Make single injection of the sample preparations.

Calculate the kavalactone concentration in the sample.

System Suitability:

The correlation coefficient of the linear regression must be ≥ 0.999 .

The resolution between desmethoxyyangonin and yangonin peaks must be ≥ 1.8 .

Retention Times (Approximate):

Methysticin 18.7 minutes

Dihydromethysticin 19.8 minutes

Kavain 21.0 minutes

Dihydrokavain 23.0 minutes

Desmethoxy-
yangonin 28.7 minutes

Yangonin 30.4 minutes

Calculations: % Individual

Kavalactone =
$$\frac{(A) (SR) (FV) (D) (F) (100\%)}{(W)}$$

Where:

A = Peak area response of the kavalactone in the sample.

SR = The response factor of the appropriate kaalactone reference standard determined by the least square fit of the calibration data.

FV = The final value of the sample preparation.

D = The dilution factor of the sample preparation (if needed).

F = The correction factor for quantitation against kavain (if needed).

Correction Factors (F):

Compound:

Methysticin 0.663

Dihydromethysticin 1.65

Kavain 1.00

Dihydrokavain 1.70

Desmethoxy-

yangonin 0.904

Yangonin 0.878

W = The sample weight (mg) (INA, 2000).

Overall chromatographic representation of INA Kavalactones given in Fig. 1.

Validation Attributes

Validation ultimately establishes documented evidences which prove a high degree of assurance that a specific process will constantly produce a herbal medicine product meeting its pre-determined specifications and quality attributes.

Apart from natural products of herbal origin of established therapeutic value, another field of interest and supportive criteria for initiating the validation programme can be of nutritional supplements where only one example, i.e. of dissolution phenomenon relevant to test requirements can be cited.

While standards for manufacturing and testing of pharmaceutical products are well established, the standards for dietary supplements are still in the developmental stages. Methods for evaluation of acceptability and stability for pharmaceuticals are provided in approved applications and are publicly available in the *United States Pharmacopeia Monographs*. The Center for Drug Evaluation and Research (CDER)

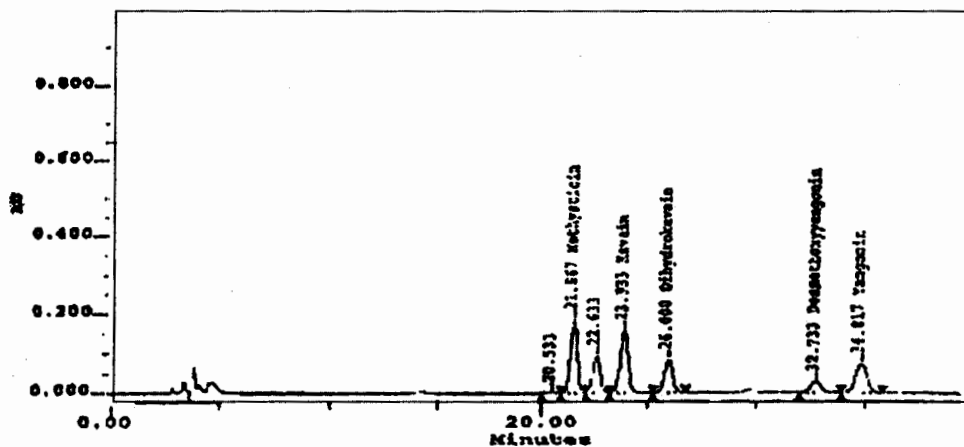


Fig. 1: Chromatogram for Kavalactones Method.

regulates both over-the-counter and prescription drugs and 21 CFR-211 (Code of Federal Regulations, 1998) provides standards for good manufacturing practices and testing. Some of the same concerns about the manufacturing of pharmaceuticals also apply to the manufacturing and testing of dietary supplements. The Center for Food Safety and Nutrition (CFSAN) regulates foods, vitamins, minerals, dietary supplements and cosmetics. Until recently, dietary supplements had little or no standards for potency, dissolution or stability (Table - 1). In 1993, in *USP 22, Supplement 8* (The United States Pharmacopeia, 1993), standards for vitamins including disintegration and dissolution tests first appeared. The *USP* section of the compendium contains monograph methods for vitamins and calcium supplements. The testing is based upon the end use and strength. If a calcium product is a compendial article and is to be used as an antacid, the test is a disintegration test. If the article is being used as a calcium supplement for the treatment of osteoporosis, the test is a dissolution method (The United States Pharmacopeia, 1995). Since the manufacturer has no control over the end use, it becomes his responsibility to see that if tested, the product would pass both tests over the shelf life of the product.

In establishing the test requirements for vitamins, the *USP* considered the degree of

difficulty of the testing and the number of active ingredients present in the formulation. A list of index vitamins and mineral's vitamins were chosen based upon solubility. It is presumed that if the least soluble item in the formulation is dissolved that the other components of the product are in solution as well. Additionally, the *USP* provides for a less work intensive test by combining aliquots from 6 tests for a single determination.

Dissolution Test Requirements

USP Classification Table

- a. Class I : Oil-soluble Vitamins.
Dissolution not required
- b. Class II: Water-soluble Vitamins
Dissolution: one index vitamin; folic acid (if present)
- c. Class III: Water-soluble Vitamins with Minerals
Dissolution: one index vitamin and one index element; folic acid (if present)
- d. Class IV: Oil- and Water-soluble Vitamins
Dissolution: one index water-soluble vitamin; folic acid (if present)
- e. Class V: Oil- and Water-soluble Vitamins with Minerals
Dissolution: one index water-soluble vitamin and one index element; folic acid (if present)
- f. Class VI: Minerals
Dissolution: one index element (The United States Pharmacopeia, 1998).

Table - 1: Significant Dates for Nutritional Supplements Test Requirements

1991 :	<i>USP Open Conference</i> on Vitamins, Minerals and Nutritional Supplements; first proposals discussed and reviewed.
1993 :	<i>USP 22 Supplement 8</i> : First standards established; requirements for initial disintegration testing; dissolution testing if disintegration failed.
1993 :	<i>USP Pharmacopeial Forum 19</i> [16] : Proposal submitted for establishing dissolution requirements for nutritional supplements.
1994 :	<i>Dietary Supplement Health and Education Act</i> (DSHEA) passed by US Congress.
1995 :	<i>USP-23 Supplement 1</i> : Dissolution testing established as requirement for nutritional supplements, including folic acid, index vitamin and index element.
1995-1998:	<i>Subsequent USP-23 Supplements</i> ; Fine-tuning of requirements, test methods and assays.
1998 :	Inclusion of botanicals in <i>USP/NF monographs</i> .

Tolerances

The requirements are met if not less than 75% of the labelled content of folic acid, and not less than 75% of the assayed content of the index vitamin or the index element from the units tested is dissolved in 1 hour.

At the present time, there is an increased concern about folic acid and its importance in the treatment and prevention of disease and a decreased risk of neural tube defect affected pregnancy. Additionally, patients are treated on other medications based upon a regular intake of folic acid-containing products in the diet. It is critical to the treatment of these other conditions that the content of these products be as labelled. Folic acid is a food additive to bread products, an ingredient in multiple vitamins, an OTC pharmaceutical product and prescription product in higher doses.

Nutritional supplement standards were first proposed in *Pharmacopeia Forum 19* (Federal Register Notice, 1997) 1993 (*Pharmacopeia Forum*, 1993) and accepted in 1995. Standards for nutritional supplements are provided as Official Monographs and General Chapters-General Test and Assays in the National Formulary section of the book (*The United States Pharmacopeia*, 1995). These include Microbial Limit Tests <2021 >, NF Section 2040 Dissolution of nutritional supplements, Weight Variation < 2091 > and Manufacturing Practices for Nutritional Supplements. These standards are very similar to those published for CGMPs for pharmaceuticals in 21 CFR 211 (Code of Federal Regulations, 1998). The standards in USP apply only to articles that are labelled "USP". These materials, if tested, must meet USP monograph standards including dissolution and potency.

As with any equipment or analytical method, **validation** is a critical part of the development package. It is the validation that demonstrates the accuracy and precision of the data. The qualification process is divided between the facility, the equipment systems,

the process and the analytical method. The facility portion of testing should include the temperature and humidity controls in the test area, demonstration of procedures that protect from contamination, the availability of a low vibration work station and reliable utilities, electrical and water.

The steps of the equipment qualification procedure should include:

1. Testing of the equipment components.
2. Development of qualification procedures or protocols.
3. Installation Qualification (IQ).
4. Operation Qualification (OQ).
5. Performance Qualification (PQ)
6. Cleaning Validation (CV).

The equipment validation protocols should:

1. Identify the critical steps in the process.
2. Provide methods to monitor the process.
3. Establish acceptance limits.
4. Control to conform.
5. Document.
6. Re-evaluate.

Processes and process controls should be qualified. Where the results of a process can not be fully verified by subsequent inspection and testing, the process should be qualified with a high degree of assurance and approved according to established procedures. Essential processing parameters should be qualified for both procedures and equipment. For equipment, these should include the use of automated systems and the verification of the stability of the dosage form while open to ambient conditions. As demonstrated in the graph of the dissolution rate of Prednisone Tablets, provided therein, when exposed for three days to high temperature and humidity, the tablets failed to dissolve (*The United States Pharmacopeia*, 1995). An automated delivery system should provide protection from light, excessive temperature and humidity.

Method validation should include the testing of the active components and the

product matrix or placebo and the market product. The test method should provide instruction to protect the product from degradation, such as "protect from light" if the article is light sensitive. The product should meet the solubility requirements for the amount of dissolution media in the container. The method should be accurate, precise and rugged. The CDER Guidance for Industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (Guidance for Industry Dissolution Testing of Immediate release Solid Oral Dosage Forms, 1997) provides information that will assist the nutritional industry as well.

Unlike pharmaceuticals, these materials do not have limits on impurities and degradants. Since most nutritional supplements are natural products or extracts thereof, it is sometimes difficult to determine what the active chemical component of the article is. The material is a complex mixture of naturally occurring substances in amounts that vary based upon season and source. Still, there are certain properties of these products that bear a similarity to pharmaceutical products and can benefit from the extensive history and knowledge of the pharmaceutical chemist.

Many nutritional supplements are compounded into solid oral dosage forms, using established tableting or capsule technology. These practices incorporate the use of starch and other materials as binders and disintegrants. Like pharmaceuticals, these preparations can be sensitive to moisture, light, oxygen and heat. The manufacture, packaging, storage and distribution chain should be developed with these sensitivities in mind. The critical conditions of temperature and humidity must be determined for the product to be safely delivered into the hands of the consumer. The critical conditions are those beyond which the product would suffer an irreversible change and not be suitable for use or meet label claim. The critical test parameters for solid oral dosage forms should include potency and dissolution

or disintegration where applicable.

For pharmaceutical products the ICH (ICH, 1994) and USP Test Conditions are as follows:

6 months accelerated 40°C/75% RH, 24 months CRT 30°C/60% RH, 24 months CRT 25°C/60% RH.

The labelled storage conditions for controlled room temperature are 15-30°C USP MKT 25. The shipping conditions are yet to be determined. At this time, there are no specific FDA requirements for the storage and testing conditions for stability studies for dietary supplements. Since the pharmaceutical test conditions for temperature and humidity are based upon climatic conditions, it is scientifically sound to use these same conditions for the testing and storage of dietary supplements.

In 1994, the Dietary Supplement Health and Education Act established new regulations for dietary supplements, including vitamins, minerals, herbs, botanicals and related products. The law also gives the FDA the right to establish CGMPs for these products. The law provides greater freedom for manufacturers to market products, providing information about the benefits in the product labeling. However, the manufacturer must exercise care that the claims do not provide for the product to cure, mitigate, treat or prevent disease. The requirements for these products are based upon the labeling claims. Consumers are encouraged to purchase products that are labeled USP, since the standards for those products are established. If a product fails to meet USP requirements over shelf life, it is considered to be mislabeled and misbranded and the FDA can take appropriate action against the firm. Nutritional supplements and vitamins are supposed to meet label claim at expiration date. Products that do not contain an expiration date are considered to have to meet label claim indefinitely. If they fail to meet label claim, they are mislabeled and

misbranded, and the agency can take appropriate action.

There is an increased need for understanding of regulation, establishment of realistic stability testing protocols and establishment of realistic expiration data using validated test methods and standards. Hanson Research is continuing to develop procedures and provide information in this area. From 1995-1998, USP 23/NF Supplement 1 to date, standards for 9 nutritional supplements have appeared in NF. NF Monographs have been published for Ginseng, Garlic, Gingko, and St. John's Wort. Many monographs are under development, including Hawthorn Leaf with Flower (Pharmacopeia Forum, 1998), Cranberry Extract (Pharmacopeia Forum, 1998), Milk Thistle (Pharmacopeia Forum, 1998), and Valerian (Pharmacopeia Forum, 1998). It is in a firm's best interest to take an active role in this process to influence the methods and standards that will impact on the products that they manufacture (Jeanne Taborsley, 2000).

Prospects in Validation

Pakistan is a country where medicinal, culinary and aromatic herbs have widely been utilized for the production of herbal medicine to be used by 80% of the populace to ward off disease and malaise. These are not in hundreds but in thousands, the phyto-therapeutic agents are blended into folkloric and pharmaceutical dosage forms to be utilized in the *Unani* and *Indusyunic* system of medicine. In recent years, many more herbal drug manufactures have given new impetus to prepare herbal based dosage forms designed through small and medium size industries, throughout the length and breadth of the country. But due to the practice or presence of non-regulatory affairs, the dosage form designs vary from industry to industry. Their consistency and quality also varies with the number of hands and virtues involved in the production and manufacturing of herbal medicine. This variation definitely is due to the non-availability of the established norms and non-compliance of validation process

based either on methods or operational parameters. The standardization or quality assurance either of primary herbal material as extract or the specified minimum level of one or more plant constituent is to be consistent in quantity and quality for the potency and efficacy from batch to batch. Further care has to be taken to analyze microbiological contaminants, minerals and metals and pesticides residue as well.

The preparation and consumption of therapeutic herbs is progressed through time from vaguely measured formula and dosage to specifically quantified amounts. Therefore, the first step in this direction is to standardize herbal extracts concentration and dosages. But the last step to test the validity of the end product dosage form is only through the validation process which caters to the recognizable quality of the product. Indeed it is necessary for the herbal product industry to ensure that validation processes are applied in the manufacturing of herbal medicine and that Validation Program Control is accessed for better quality phytopharmaceuticals. This will provide the credibility in the reputation and growth of herbal medicine for the foreseeable future (Daniel B., 1988).

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