International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 6 Issue 3, March-April 2022 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

WHO & ICH Guidelines for the Assessment of Herbal Drug

Ms. Bhadane Suvarna[1], Dr. Takarkhede Smita[2], Ms. Kakade Pooja[3], Ms. Jaiswal Sangeeta[3], Ms. Kanaujiya Shreya[3], Ms. Khan Alqama[3]

[1]Faculty of Ideal College of Pharmacy and Research Kalyan Mumbai,
[2]Principal of Ideal College of Pharmacy and Research,
[3]Student of Ideal College of Pharmacy and Research,
[1, 2, 3]Ideal College of Pharmacy & Research, Kalyan Affiliated by University of Mumbai, Maharashtra, India

ABSTRACT

The medicinal plant and herbal drugs products are widely used for thousands of years in all over the parts of the world. The word "herbal drugs" denoted plant parts or plants.

That is converted into phytopharmaceuticals by means of straight forward processes including harvesting, drying, and storage. In recent few decades, growth and recognition of herbal medicine and plant products have taken a big share of healthcare.

There's the increasing awareness and general acceptability of the use of herbal drugs in today's practice Although, most of these applications are unorthodox, it's however known fact that all over 80% of the world population are depends on herbal medicine and products for healthy living Where standardization and control with proper integration of recent scientific techniques and lore is incredibly important. This rise within the utilization of herbal product has also given to numerous forms of adulteration and abuse of the products leading to consumers and manufacturers disappointment. The challenge is innumerable and making the worldwide herbal market unsafe Evaluation of herbal drug showing an important and vital tool within the formulation of high-quality herbal products. Herbal drug technology mainly used for converting botanical materials into medicines.

KEYWORDS: *WHO parameters, ICH guidelines, Standardization, Herbal drug*

How to cite this paper: Ms. Bhadane Suvarna | Dr. Takarkhede Smita | Ms. Kakade Pooja | Ms. Jaiswal Sangeeta | Ms. Kanaujiya Shreya | Ms. Khan Alqama "WHO & ICH Guidelines for the Assessment of Herbal Drug" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-6 | Issue-3, April 2022, pp.549-559, URL: www.ijtsrd.com/papers/ijtsrd49571.pdf

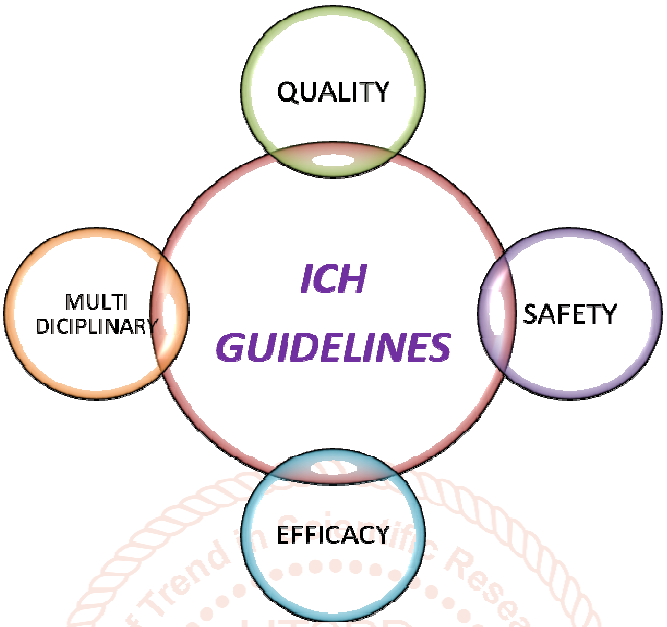
IJTSRD49571

INTRODUCTION

The International Conference on Harmonisation (ICH) is established in 1990 for Registration of Prescription drug for Human Use World Health Organization (WHO) Established in 1948 for international health matters and public health has set certain standard for herbal drugs. The purpose is to get recommendations on ways to understand greater harmonisationin the interpretation and application of technical guidelines and requirements for product registration thus on reduce or obviate the necessity to duplicate the testing carried outthought out the analysis and development of latest me I", "C", "H" During exceedingly very manner which embodies the letters in an summary human form. For world harmonization WHO and ICH import specific guidelines for the assessment of the protection, efficacy and quality of herbal medicines are of almost importance. The most colour of the logo or emblem is blue, a color often used with healthcaredicines. Standardization of drug means to confirmation of its identity, quality and purity throughout all phases of its cycle. The process of evaluation of the quality and purity of crude drugs by means of various parameters like morphological, microscopically, physical, chemical and biological observations is called standardization. WHO and ICH imported guidelines for the assessment of herbal drugs and medicine. This are approved guidelines by a WHO and ICH for herbal drugs and medicine to discover the quality, efficacy and stability for the betterment used and approved. [2][4]

Objective

- Harmonization of legislative & technical requirements.
- Mutual acceptance of data between Europe, Japan & US.
- To reduce cost of research work duplications.
- To reduce time frame for international marketing of newer medicine after approval
- To maintain & formulate guidelines on quality, safety & efficacy-based regulations, for client & patient benefits. [2]



1. Quality Guidelines:

Harmonisation attainment within the Quality category include important milestones like the carrying of stability studies, determining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality supported Good Manufacturing Practice (GMP) risk management.[8]

S. NO	GUIDELINES
1	Q1A-Q1F Stability:
	Q1A: Stability testing of latest and up to date drug substances and products
	Q1B: Stability testing: photo stability testing of latest drug substances and products.
	Q1C Stability testing for new dosage forms
	Q1D Bracketing and matrixing designs for stability testing of recent drug substances and products
	Q1E Evaluation of stability data
	Q1F Stability data package for registration applications in climatic zones III and IV
2	Q2 Analytical validation:
	Validation of analytical procedures
3	Q3A-Q3D Impurities:
	Q3A Impurities in new drug substances
	Q3B Impurities in new drug products
	Q3C Impurities: Guidelines for residual solvents
	Q3D Impurities: Guidelines for elemental impunities
4	Q4A-Q4B Pharmacopeia's:
	Q4A: Pharmacopeia Harmonization
	Q4B Evaluation and recommendation of pharmacopeial texts to be used within the ICH regions
5	Q5A-Q5E Quality of biotechnological products:
	Q5A Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
	Q5B Analysis of expression construct in cells used for production of r-DNA derived protein products

	Q5C Stability testing of biotechnological/ biological products
	Q5D Derivation and characterization of cell substrates used for production of biotechnological/ biological products
	Q5E comparability of biotechnological / biological products subject to changes in their manufacturing process
6	Q6A-Q6B Specifications:
	Q6A Test procedures and acceptance criteria for brand spanking new drug substances and new drug products: Chemical substances
	Q6B Test procedures and acceptance criteria for biotechnological/ biological product
7	Q7 Good manufacturing practices for Active pharmaceutical ingredients
8	Q8 Pharmaceutical development
9	Q9 Quality risk management
10	Q10 Pharmaceutical quality system
11	Q11 Development and manufacture of drug substances (Chemical entities and biological entities

2. Safety Gudelines:

ICH has also make a comprehensive set of safety guidelines to reveal and avoid potential risks like carcinogenicity, reprotoxicity and genotoxicity. [8]

S.NO	GUIDELINES
1	S1A-S1C Carcinogenicity studies:
	S1: Rodent carcinogenicity studies for human Pharmaceuticals
	S1A: Need for carcinogenicity studies of Pharmaceuticals
	S1B: Testing for carcinogenicity of Pharmaceuticals
2	S2 Genotoxicity studies
	S2 (R1) Guidance on genotoxicity testing and data interpretation for Pharmaceuticals intended to be use of human
3	S3A-S3B Toxic kinetics and pharmacokinetics:
	S3A note to aware for guidance on Toxicokinetics: The assessment of systemic exposure in toxicity studies
	S3B Pharmacokinetics: Guidance for repeated dose tissue distribution studies
4	S4 Toxicity testing:
	S4 Duration of chronic testing in animals (Rodent and non-rodent toxicity testing)
5	S5 Reproductive toxicology:
	S5 Detection of toxicity to reproduction for medicinal products and toxicity to male fertility
6	S6 Biotechnological products:
	S6 Preclinical safety Evaluation of biotechnology derived Pharmaceuticals
7	S7-S7B Pharmacology studies:
	S7A Safety pharmacology studies for human Pharmaceuticals
	S7B The non-clinical evaluation of the potential for delayed ventricular repolarization by human Pharmaceuticals
8	S8 Immunological Studies:
	S8 Immunotoxicity studies for human Pharmaceuticals
9	S9 Nonclinical evaluation for anti-cancer Pharmaceuticals
10	S10 Photo safety evaluation of Pharmaceuticals

3. Efficacy Guidelines:

Efficacy guidelines are concerned with the planning, carrying, and safety and reporting of clinical trials. It gives information about biotechnological methods such as novel types of medicines. And therefore the use of pharmacogenomics techniques to supply better targeted drug. [8][19]

S. No	Guideline
1	E1 Clinical safety for drugs employed in long run treatment
2	E2A-E2F Pharmacovigilance
3	E3 Clinical study reports
4	E4 Dose response studies
5	E5 Ethnic factors
6	E6 Good clinical practice
7	E7 Clinical trials in geriatric population
8	E8 General Consideration for clinical trials
9	E9 Statistical principles for clinical trials
10	E10 choice of control group in clinical trials
11	E11 Clinical trials in paediatric population
12	E12 Clinical evaluation by therapeutic category
13	E14 Clinical evaluation
14	E15 Definitions in pharmacogenetics/ Pharmacogenomics
15	E16 Qualification of genomic biomarkers
16	E17 Multi regional clinical trails
17	E18 Genomic sampling methodologies

4. Multidisciplinary Guidelines:

Multidisciplinary Guidelines: Multidisciplinary Guidelines provide information about Common Technical Document (CTD) medical terminology (MedDRA), and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).[8]

S.NO	GUIDELINES
1	M1-MedDRA terminology Medical dictionary for regulatory activities.
2	M2 Electronic standards
3	M3 Non clinical safety studies
4	M4 Common technical document
5	M5 Data elements and standers for drug dictionaries
6	M6 Gene therapy
7	M7 Genotoxic impurities
8	M8 Electronic common technical document (eCTD).

Guidelines:

Quality guidelines

1. Q1A-Q1F Stability: The guideline seeks to exemplify the core stability information package for brand new drug substances and product, but leaves sufficient flexibility to comprehend the range of various sensible things that will be encountered thanks to specific scientific concerns and characteristics of the materials being evaluated.

Drug substances

Information on the stability of the drug substance is an important part of the systematic approach to stability analysis.

Includes

- Stress testing
- Selection of batches
- Container closure system
- Specification
- Testing frequency
- Storage condition
- Stability commitment
- Evaluation
- Statements
- labelling

Drug product

The design of the formal stability studies for the drug product should be based on knowledge of the behaviour and

Properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical

Formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the

Formal stability studies should be stated.

Includes

- Photo stability testing.
- Selection of batches.

- Container closure system.
- Specification.
- Testing frequency.
- Storage conditions.
- Stability commitment.
- Evaluation.
- Statements
- Labelling.

2. Q2 Analytical validation:

The validation of analytical procedures is based on four most common types are

- Identification tests,
- Quantitative tests for impurities content,
- Limit tests for the control of impurities
- Quantitative tests of the active moiety in Samples of drug substance or drug product or other alternate component in the drug product.

3. Q3A-Q3D Impurities:

This document is meant to provide guidance for registration applications on the content and qualification of impurities in new drug substances created by chemical synthesis and not previously registered in a region or member state. It is not supposed to use new drug substances used throughout the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological, biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin.

4. Q4A-Q4B Pharmacopoeias:

This document describes a process for the evaluation and recommendation by the Q4B Expert Working Group (EWG) of selected pharmacopoeia texts to facilitate their recognition by regulatory authorities for use as interchangeable in the ICH regions.

5. Q5A-Q5E Quality of biotechnological products:

This document is concerned with testing and analysis of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin that is example mammalian, avian, insect and outlines data that should be submitted in the marketing application and registration package. The purposes of this document to express virus excludes nonconventional transmissible agents like those associated with Bovine Spongiform Encephalopathy (BSE) and scrape. Applicants are focussed to discuss issues associated with BSE with the regulatory authorities.

Three principal that are complementary approaches have evolved to control the potential viral contamination of biotechnology products:

- Selecting and testing cell lines and other raw materials that including media components,
- Undesirable viruses which may be infectious and pathogenic for humans;
- Assessing the capacity of the production processes to clear infectious viruses;
- Testing the product at appropriate steps of production for absence of contaminating infectious viruses.

6. Q6A-Q6B Specifications:

The quality of the drug products and drug substances can be determined by their design, development, in-process controls, GMP controls, and process validation, and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, i.e., those tests, procedures, and acceptance criteria which play an important role in assuring the quality of the new drug substance and new drug product at the release and throughout shelf life. Specifications are an important component of quality assurance, but it is not only Component. All of the considerations mention above are necessary to ensure consistent production of drug substances and drug products of high quality.

7. Q7 Good manufacturing practice guide for active pharmaceutical ingredients:

This document is to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate and proper system for managing quality.

8. Q8 (R2) Pharmaceutical development:

The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline to a particular type of product, applicants can consult with the appropriate regulatory authorities.

9. Q9 Quality risk management: principles of quality risk management are:

- The analysis of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

10. Q10 Pharmaceutical quality system:

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances that's active pharmaceutical ingredients and drug products as well as biotechnology and

biological products, throughout the product lifecycle. The elements of ICH Q10 should be applied in a manner that is applicable and proportionate to each and every of the product lifecycle stages, recognizing the variations among, and also the completely different goals of each stage.

11. Q11 Development and manufacture of drug substances (chemical entities and Biotechnological/biological entities):

A company will prefer to follow completely different approaches in developing a drug substance. For the aim of this guideline, the terms "traditional" and "enhanced" are used to differentiate two potential approaches. In a traditional approach, set points and operation ranges for method parameters are defined and the drug substance control and management strategy is usually based on demonstration of process reproducibility and testing to meet established acceptance criteria.[18] In an associate increase approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes and develop appropriate control strategies applicable over the lifecycle of the drug substance which may include the establishment of design space. [8][9].

Safety guidelines:

1. S1A-S1C Carcinogenicity studies:
2. S2 Genotoxicity studies

The objective of this guideline is to outline the conditions underneath that carcinogenicity studies, ought to be conducted to avoid the supernumerary use of animals in testing, and to provide consistency in worldwide restrictive assessments of applications. It is expected that these studies are performed in a very manner that reflects presently accepted scientific standards [9] This steerage replaces and combines the ICH S2A and S2B tips the aim of the revision is to optimize the quality genetic materia medica battery for prediction of potential human risks, and to supply steerage on interpretation of results, The ultimate goal of rising risk characterization for malignant neoplastic disease effects that have their basis in changes within the genetic material. The revise internationally agreed upon standards for follow-up testing and interpretation of positive ends up invitto and in vivo within the customary genetic materia medica battery, as well as assessment of non-relevant findings [9]

3. S3A-S3B Toxico kinetics and pharmacokinetics:

Objectives:

- To describe the general exposure achieved in animals and its relationship to dose level and therefore the time course of the toxicity study.
- To relate the exposure achieved in toxicity studies to pharmacological medicine findings and contribute to the assessment of the relevance of these findings to clinical safety.
- To support the selection of species and treatment program in non-clinical toxicity studies.
- To provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies.

4. S4 Toxicity testing:

This guidance has been provided for the development of medicinal products with the exception of these already covered by the ICH Guideline on Safety Studies for Biotechnological Products, example: organism antibodies, Monoclonal antibodies, recombinant DNA proteins.

5. S5 Reproductive toxicology: This guideline applies to any or all prescription drugs together with biopharmaceuticals, vaccines and their novel essential ingredients for infectious diseases, and novel excipients that are part of the ultimate pharmaceutical product. This guideline does not apply to cellular therapies, factor therapies and tissue-engineered products. The methodological principles is to study design, dose Choice and species selection, etc. outlined in this guideline apply to all compounds for which the conduct of reproductive and developmental toxicity studies is important. [9]
6. S7-S7B Pharmacology studies:

This guideline was developed to help and protect clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals, whereas avoiding excess use of animals and different resources. This guideline usually applies to new chemical entities and biotechnology derived products for human use [7] [8]

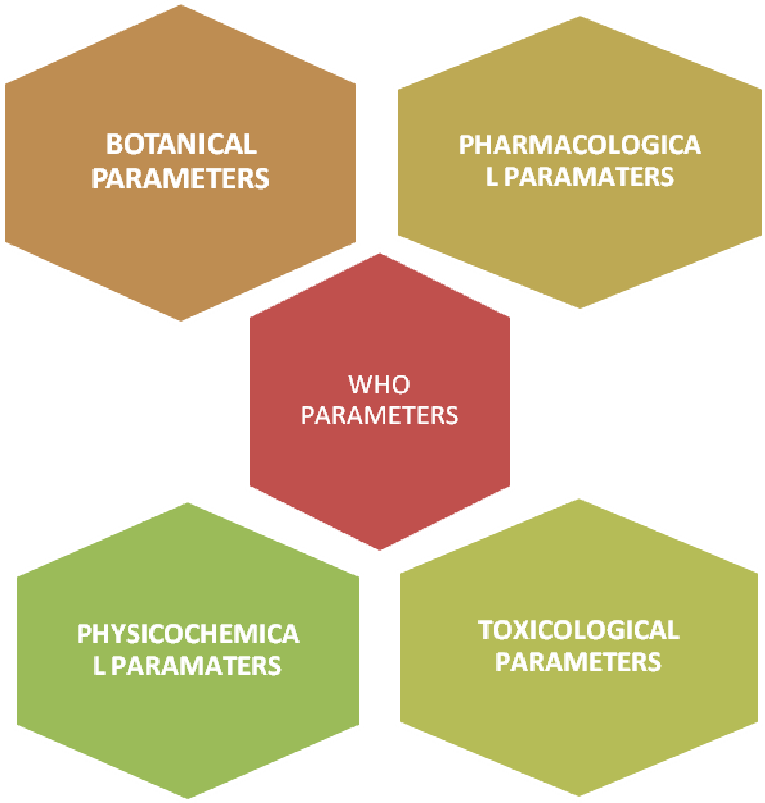
Efficacy guidelines:

1E1-E18: The work and process carried out by ICH under the Efficacy guidelines is related with the safety reporting of clinical trial and design. It additionally covers novel varieties of medicines derived from biotechnological processes and also the use of genetics and pharmacogenomics techniques to produce higher targeted medicines. Clinical studies of medicinal products are conducted to provide information that can improve access to safe and effective products with appropriate impact on patients, while protecting those participating in the studies. This guideline provides guidance on the clinical development lifecycle, that including designing quality into clinical studies, considering the

broad range of clinical study designs and data sources used. [8][6]

Multidisciplinary Guidelines:

IMI-M8: It includes the ICH medical terminology, the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI). The objective under this guidelines is to define logical electronic communication standards for communication with Regulatory Authorities. In effect, this means the adoption of those international standards essential for the direct communication of all information required in a submission and all associated information (primarily safety) required as part of the regulatory process. Harmonisation of the guidance for nonclinical safety studies will help to explain the current recommendations and reduce the likelihood that substantial differences will exist among regions. [8][6].



A. Botanical Parameters

1. Sensory evaluation-Visual macros copy, Colour, Odour, Taste, Fracture are the common tests conducted for identification of the crude drug [3]
2. Foreign matter-It has to be determined if the foreign matter is
   - Organic (Moulds, Insects, Animal waste matter etc.) or
   - Inorganic (Stone, soil etc.).

Foreign matter is taken into account as

Methods to determine the foreign organic matter-

- Manual method

Procedure:

FOR CRUDE DRUG:

1. Take weighed quantity of crude drug (500 G root\stem\dark, 250 G leaves flowers\ seed fruit, 50 G cut plant material).
2. Spread it in a thin layer and sort the foreign material by using magnifying lens (10x) or suitable sieve or by visual inspection.
3. Pass the remaining sample through a sieve no. 250 to remove dust (mineral admixture).
4. Weigh the portion of sorted foreign matter and determine % w/w of it.
5. If foreign matter resembles plant material, take pooled sample and apply physical /chemical test or microscopy. Determine the proportion of foreign matter from fail to respond to the test.

FOR WHOLE DRUG:

1. Weigh 100 to 500 g of the sample (or the quantity specified in the monograph of the drug)
2. Spread uniformly the sample on a white tile or a glass plate without overlapping
3. Inspect the sample with naked eyes or by means of a lens (3x or above).
4. Separate the foreign organic matter manually
5. After complete separation, weigh the matter and determine % w/w present in the sample

➢ Lycopodium spore method

Lycopodium family is lycopodiaceae species spore of club moss having uniform dimensions (94 m) Wallis determined number of spores present in milligram by experiments average to be 94000

Procedure:

1. Dry the powdered drug at 105°C and determine its steady weight at room temperature.
2. Weigh accurately powdered material and Lycopodium spores and mix them Proportion of 2:1 powdered drug to Lycopodium has been found to be satisfactory. Mix them on a glass plate with a flexible spatula.
3. Make a thin smooth paste by adding a suspending medium (oil or glycerine: tragacanth mucilage: water, 2:1:2) Transfer the paste into a stoppered tube by washing quantity of suspending media.
4. Adjust the final volume by suspending fluid such that about 10 to 20 spores may be present in a field of 4 mm objective.
5. Oscillate the tube gently to get a uniform suspension.[21]
6. Place a drop on slide, spread with a needle, put coverslip and count the characteristics particles of the organic matter as well as the Lycopodium spores in the field
7. Make one more slide in the same way and count 25 fields
8. Prepare another suspension as described above, prepare two more slides and count 25 fields each for both preparations as above.
9. Determine the average of 4 sets of counts (4 x 25 = 100 fields in all).and also the percentage of moisture present from the first step. Calculate the number of characteristics particles present in one mg of the powder dried at 105°C Determine in a similar way the number of characteristic particles per mg of the pure foreign matter, calculated with reference to the material dried at 105° (If this number can be obtained from the literature a special experiment is unnecessary).

Calculate the percentage of foreign organic matter from the formula

Percentage of foreign organic matter

$$\frac{n \times w \times 94000 \times 100}{s \times m \times p}$$

Where,

n = number of characteristics particles in 25 fields.

s = number of spores in the same 25 fields

w = weight in mg of Lycopodium taken.

m = weight in mg of the sample (calculated on the sample dried at 105°C).

p = number of characteristics particles per mg of the pure foreign matter.

(Calculate on the material dried at 105°C).

94,000 number of spores per mg of Lycopodium

3. Microscopy test -Identification of histological characters (under low and high power).

B. Physicochemical Parameter's

1. Chromatographic fingerprint-

Separation, identification, impurity detection and assay of herbal drug within the formulation or in extract are carried out by following methods: -

HPTLC, HPLC/Densitometry chromatography, GLC, TLC test

Importance-The herbal drug shows variability in its chemical constituents consistent with various locations/weather. To avoid any erroneous identification action fingerprint remains the assessment of choice.

2. Ash value-

The types of ash determined are Total ash, insoluble in acid and soluble in water.

Ash value is used to determine the quality and purity of the drug and to establish its identity.

Ash contains inorganic radicals lie phosphates, carbonates, and silicates of sodium, potassium, magnesium, calcium etc. These are present in definite amount during a particular crude drug, hence quantitative determination in terms of varied ash values helps in their standardization. Ash value is used to determine foreign inorganic impurity. [3]

Total Ash Value-The method of total ash is meant to determine the amount of material that remains after ignition. Ash is assessed as physiological ash which is derived from the plant part itself and non-physiological ash which is that the residue after ignition of extraneous matter (e.g. sand and soil).It is carried out at low temperatures possibly because alkali chlorides, which a volatile at low temperatures, may be lost. The total ash consists may be carbonates, phosphates, silicates and silica.

Acid insoluble ash- Inorganic variables like calcium oxalate, silica, and carbonate content of the crude drug affects Total cash value. Acid soluble ash is determined by removed variables by treating with acid if its soluble in hydrochloride acid Same as the Acid insoluble Ash, Water soluble ash and sulphated ash are also evaluated

3. Extractive values

➢ Its useful for evaluation of a crude drug. It gives a thought about the nature of the chemical

constituents present in crude drug. Useful for constituents extracted with the solvent used for extraction. Employed for material that far no suitable chemical or biological assay exists. It are often done by following methods:

- Cold maceration,
- Hot extraction

4. Moisture content and volatile matter test -

The Drug moisture content should be minimized to prevent decomposition of crude drug either due to chemical change or microbial contamination.

The moisture content is decided by heating a drug at 105˚c in an oven to a constant weight.

E.g. – Aloe should have moisture content not more than 10% w/w Moisture

Content can be determined by following methods -

- Gravimetric
- Volumetric
- instrumental

Gravimetric method-Loss on Drying,

Volumetric-Azeotropic Toluene distillation method,

Instrumental- GC, NMR etc.

Volatile oil content- Essential oils are the liquid components of the plant cells, immiscible with water, volatile at ordinary temperature and may be steam distilled at ordinary pressure. Many herbal drugs contain Essential oil which is employed as flavouring agent.

For the drugs containing volatile constituents, toluene distillation method/steam distillation method is used to determine the volatile oil contents.

C. Pharmacological Parameter's

1. Bitterness value-

- Medicinal plants having strong bitter taste are therapeutically used as appetizing agents .The bitterness is determined by comparing the threshold bitter concentration of an extract material with that of quinine hydrochloride.[11]
- The bitterness value unit is equivalent to the bitterness of a solution containing 1gm of quinine hydrochloride in 2000ml Water.

Formula- Bitterness value in unit pee gm. $= \frac{2000 \times C}{A \times B}$

Where,

A. the concentration of the stock test solution (S.) (Mg/ml).

B. the volume of test solution S, (in ml) in the tube with the threshold bitter concentration,

C. C-the volume of quinine hydrochloride R (in mg) in the tube with the threshold bitter concentration.

2. Haemolytic property-

- Many medicinal plant materials, of the families Caryophylaceae, Sapindaceae, and Dioscoreaceae contain saponins.
- The main property of saponins is their ability to cause haemolysis

Formula: $1000 \times \frac{a}{b}$

Where,

1000-the defined haemolytic activity of saponin R in relation to ox blood

A. quantity saponin R that produces total haemolysis (g)

B. quantity of plant material that produces total haemolysis (g)

3. Astringent property-

- It is determined by amount of tannins present in the drug Tannins (or tanning substances) are substances capable of turning animal hides into leather by binding proteins to form water insoluble substances that are resistant to proteolytic enzymes. This process, when applied to living tissue, is called as an "astringent" action.
- tannins is mixtures of polyphenols that are difficult to separate and crystallize complex in nature [14]

4. Swelling Index-

- The swelling index is the volume occupied by 1 gram of swollen material
- Its determination is based on the addition of water or a swelling agent as shown in the test procedure for each individual plant material (either whole, cut or pulverized).
- It gives an idea content of the drug i.e. mucilage [12]

5. Foaming agent-

Procedure:

- Take 1g of coarse powder of the plant material in a 500 ml conical flask
- Add 100 ml of boiling water and maintain moderate boiling for the 30 minutes.
- Cool and filter
- Collect the filtrate decoction in a 100 ml volumetric flask and make up the volume is 100ml
- Pour the decoction into 10 stoppered test tubes (height 16 cm, diameter 16 mm) as 1 ml, 2 ml, 3 ml, etc. up to 10 ml.
- 10 ml by adding quantity of water and stopper the tubes.

- Shake test tubes for 15 seconds (two shakes per second).
- Stand for 15 minutes test tube and calculate the height of the foam.

D. Toxicological Parameters

1. Arsenic: Stain produced on HgBr paper in comparison to standard stain.
2. Pesticide residues: Includes total organic chloride and total organic phosphorus.
3. Heavy metals: Like cadmium and lead.
4. Microbial contamination: Total viable aerobic count of pathogens: Salmonella, P. aeruginosa and S. aureous.[20]
5. Aflatoxins: By TLC using standard aflatoxins (B_1, B_2, G_1 and G_2).
6. Radioactive contamination.

- Arsenic or other any heavy metal is contaminated with medicinal plant then cause many serious effect such as environmental pollution and traces of pesticides. Arsenic, Lead, cadmium is identified by the limit test or it by the lead and cadmium may be determined by the inverse in voluntary or by the atomic emission spectrophotometry.[12]
- The maximum amount of metal present in medicinal plant is

Lead contains 10mg/kg
Cadmium contains 0.3mg/kg

- Determination of pesticide

Residue it is does not contain more than 1%

Pesticides per kg of plant material i.e. (ARL) is calculated by the maximum acceptable daily intake of the pesticides for human that i.e. (ADI) as recommended WHO and means daily intake i.e. (MDI) of the medicinal plant material

$$ARL = \frac{ADI \times E \times 60}{MDI \times 100}$$

ADI = maximum acceptable daily intake of pesticide (mg/kg of body weight)

E=extraction factor, which determines the transition rate of the pesticide from the plant material into the dosage form;

MDI mean daily intake of medicinal plant product.

- The radionuclides is released into the environment because the nuclear accident might include a long lived and short lived fission products, activation product, actinides

Conclusion:

Harmonization achievements within the quality space embody important milestones like the conduct of stability studies, process relevant thresholds for impurities testing and a lot of versatile approach to pharmaceutical quality supported smart producing apply (GMP) risk management in herbal product. The WHO guidelines are followed all over the world but the need of the hour is to update these principles with application of newer methods of analysis. The Guidelines Review Committee make sure that WHO tips are of a high method quality and are developed through a clear, evidence-based decision-making method. The herbal drug assessment in Ayurveda is about the whole drug rather than concentrating on the active principles or phytoconstituents, thus finer methods of standardization should be developed. Herbal drug a rigorous quality assurance method that helps to confirm and each printed guideline is trustworthy, impactful and meets the best international standards. As Ayurvedic drugs are also included in the Drugs and Cosmetics Act, 1940 the drugs have to be safe and effective.

Acknowledgement

We would like to express our sincere gratitude towards project guide & friends, who gave us the appropriate guidance and encouraged us to carry out work on this review article

References

[1] Introduction to the ICH [2014] from: www.ich.org/fileadmin/Public Web...ICH/.../Iintroduction_to_ICH.pdf

[2] WHO_WORLD_HEALTH_ORGANIZATION _GUIDELINES_FOR_STANDARDIZATION _OF_HERBAL_DRUGS

[3] KR Khandelwal, [2013] Practical Pharmacognosy, 2nded, Nirali Prakashan, Pune, 23.1-23.4.

[4] Quality assessment of herbal preparations as precondition of pharmacological and clinical studies Phytomedicine 1996; 2: 193-198 look

[5] International Drug Monitoring the Role of National Centres. WHO Technical Report Series, No. 498, Geneva.

[6] Molzon Justina A., US Food and Drug Admistration, The value and benefits of ICH to drug regularity authorities- Advance harmonization for better health.

[7] International Harmonisation of the Regulation of New Pharmaceutical Drugs [Online]. [cited 2014 Apr 30]; Available from:

URL:http://www.whp-apsf.ca/en/documents/who_benefits.html

[8] ICH quality implementation working group, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [2011]. Geneva: ICH Secretariat

[9] International Conference in Harmonisation. Harmonised Tripartite Guideline: Immunotoxicity Studies for Human Pharmaceuticals S8. [2005]. ICH; [cited 2019 Sept 13].

[10] Q&A procedure, ICH Secreteriat. [2011 Dec]Switzerland: ICH Secretariat Available from: http://www.ich.org/about/process-of-harmonisation/qa-procedure.html

[11] DRUGS Jyoti Gaval.[August 2015] WHO (WORLD HEALTH ORGANIZATION) GUIDELINES FOR STANDARDIZATION OF HERBAL

[12] Anonymous, [2010] Indian Pharmacopoeia. Vol-3, Government of India, Ministry of Health and Family Welfare, New Delhi p. 2467-2472.

[13] Formal ICH procedure, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. [2011]. Geneva 20, Switzerland: ICH Secretariat; Available from: http://www.ich.org/about/process-of

[14] Adamczyk, B., Simon, J [2017] Tannins and their complex interaction with different organic nitrogen compounds and enzymes: old paradigms versus recent advances. Chemistry Open 6 (5), 610-614. https://doi.org/10.1002/open.201700113,

[15] ICH guideline Q4B Annex 4B on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on Tests for specified micro-organisms [Step 5] Legal effective date: 01/06/2009 EMEA/CHMP/ICH/308817/2008.

[16] Arunachalam A, Shankar M. Stability studies. Asian J Pharm Anal Med Chem 2008;1:184-95

[17] WHO. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. World Health Organization, Geneva. 2002c. EMEA.

[18] Arun Rasheed, AReview onstandardization ofherbal formulations, Inter. J. of Phytotherapy / Vol. 2 / Issue 2 /2012 / 74-88.2.

[19] Guideline on Clinical Evaluation of Cardiovascular Safety [Guideline-0193-02]

[20] Iqbal Ahmad, FarrukhAqil, and Mohammad Owais. Modern Phytomedicine, Turning Medicinal Plants into Drugs WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim fGermany 2006 p.26 53

[21] Joshi S, Aeri V, Practical Pharmacognosy. 1st edition, Frank Bros. & Co. New Delhi; 2009: 211-212.