Standardization and Quality Control Parameters Required For Herbal Medicine

Prepared for:

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Introduction

Apart from ayurvedic and unani systems of medicine, herbal medicine is a modern approach of ancient medicinal practice. Now a day's herbal medicine is addressing special interest of western world. It has got noticeable popularity among the developed worlds. Since most of the herbal medicines are standardized extracts, it is possible to identify and sometimes quantify the active principle. Therefore, the quality control process for herbal medicine very much resembles to the conventional medicine. Moreover, the dosage forms have similarities to the conventional modern medicines. Moreover, the dosages forms have similarities with the conventional medicines.

Considering the developing stage of herbal sector in Bangladesh, we tried to define the quality control parameters essentials for manufacturing and standardization of herbal medicines. The manufacturer should have the equipments and ability to operate the quality control systems depending on the dosage form available. Moreover, the total QC equipments can be accommodated phase wise.

To recommend quality control parameters for herbal medicines we have taken the references of World Health Organization and European Medicine Agency. Enclose (d in the appendix).

Basically quality control of herbal materials starts from cultivation of the herbs to the delivery of finished products. Considering the practicality we have defined the quality control parameters for herbal raw materials and finished products.

Here, we also have kept multiple options for quality control. Any company can use one or more options for controlling the quality of their products. Moreover, small companies can get the opportunity to develop facilities for quality control operation (process & equipments) for a defined time period.

Definition

A. Herbal medicines

These include herbs, herbal materials, herbal preparations and finished herbal products.

B. Herbs

Herbs include crude plant material such as leaves, flowers, fruits, seeds, stems, wood, barks, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

C. Herbal materials

Herbal materials are either whole plants or parts of medicinal plants in the crude state. They include herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir baking with honey, alcoholic beverages or other materials.

D. Herbal preparations

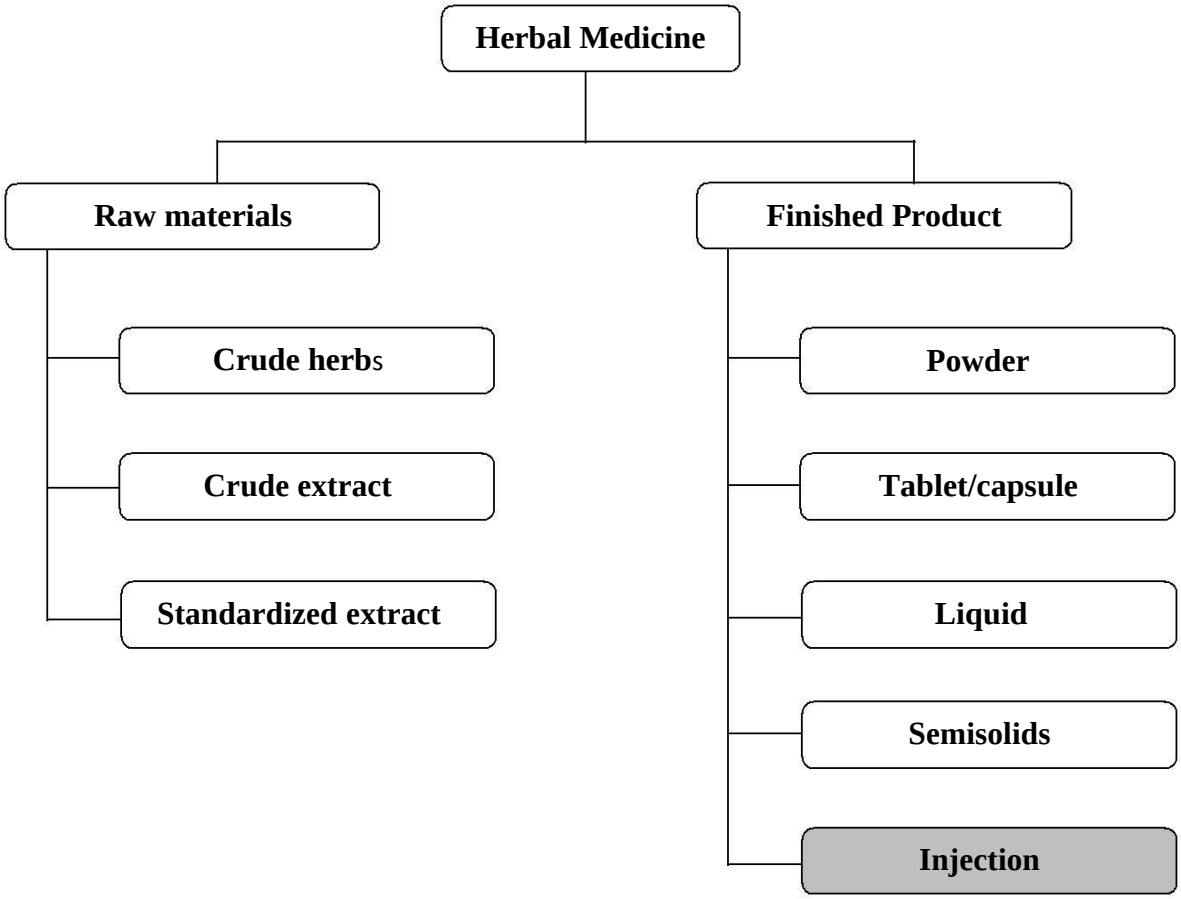
Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials or extracts, tinctures and fatty oils, expressed juices and processed exudates of herbal materials. They are produced with the aid of extraction, distillation, expression, fractionation, purification, concentration, fermentation or other physical or biological process. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

E. Finished herbal products or herbal medicinal products

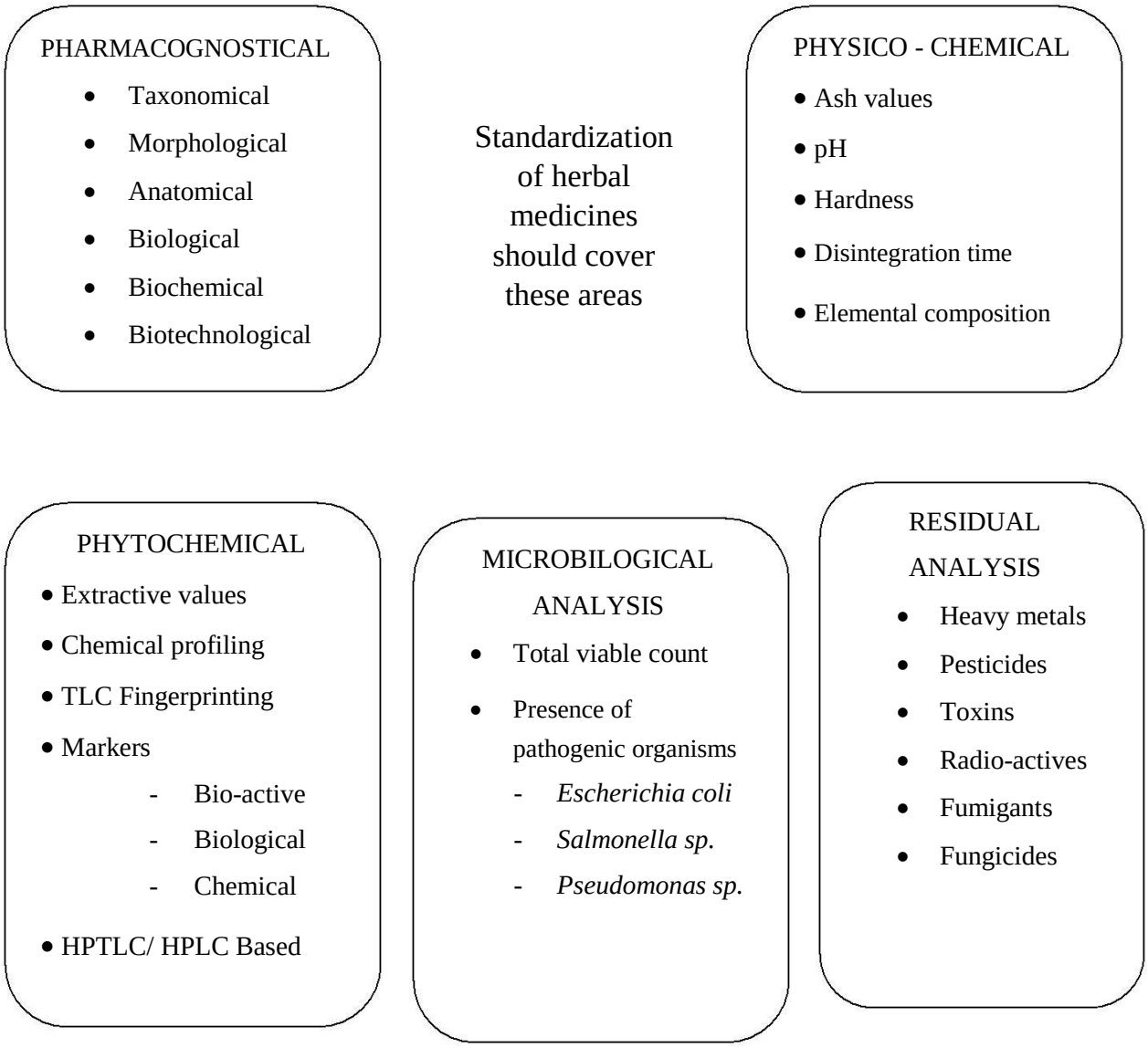
Medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations. They may consist of herbal preparations made from one or more herbs. If more than one herb is used, the term **mixed herbal product** can also be used. They may contain excipients in addition to the active ingredients. In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients, which are not of plant origin (e.g. animal materials and mineral materials).

Note: Generally however, finished products or m substances is added, including synthetic compounds are not considered to be herbal.

Segments for Quality Control



Standardization Parameters



Types of Herbal Medicines/Medicinal Products and Quality Control parameters

1. Crude Herbal materials (considered "B" in the definition part)

Quality control parameters –

- Authentication –

  Each and every step needs to be authenticated

  - area of the collection
  - parts of the plant collection
  - the regional situation
  - botanical identity
  - microscopic and
  - histological analysis

  If all or any of the parameters can authenticate the material then authentication works should be considered accomplished.

Tests and specifications of crude herbal materials are as follows

Test	**Specification**
Appearance	Qualitative evaluation of the plant source, parts used, and its condition; e.g. whole plant, bark, leaves, dry or green etc.
Characteristics	May be evaluated according to its organoleptic characteristics
Moisture content	Should be specific according to the type of plant or plant material/part
Identification/assay	Macroscopic: Must comply with the standard specifications. Microscopic: Must comply with the standard specifications. UV spectroscopy: comply with the absorption bands test after extraction Chromatographic: TLC, HPTLC, HPLC, Densitometric evaluation through evaluation of a values or retention time of the reference and test sample; comparison with the fingerprint of test and reference
Foreign matter	Must comply with the standard specifications
Total Ash	Must comply with the standard specifications
Acid insoluble ash	Must comply with the standard specifications
Water soluble material	Must comply with the standard specifications
Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil

Microbial Contamination test	Total aerobic microbial count: Not more than 10^7 CFU/g or CFU/ml Total combined yeast and mold count: Not more than 10^5 CFU/g or CFU/ml *Escherichia coli:* Not more than 10^3 CFU/g or CFU/ml *Salmonella:* Nil (1g or 1ml) *Staphylococcus aureus*: Nil (1g or 1ml) *Clostridia*: Nil (1g or 1ml) *Pseudomonas:* Nil According to the type of organisms should follow specifications of standard monograph
Aflatoxins/ Mycotoxins	Should follow standard monograph (BP/USP/WHO/EMA guidelines); i.e. Aflatoxin B1: Not more than 2µg/kg, Sum of Aflatoxins B1, B2, G1, G2): not more than 4ppb.
Pesticide Residues	Must comply with the standards recommended by standard monograph (USP/WHO/EMA guidelines).
Assay	Quantitative measure of the marker compound(s) in the test sample in comparison to reference compound(s) preferably by HTLC/HPLC/GC/ LC-MS by any suitable methods.

2. Herbal materials/Extract/Herbal preparations (considered C & D. in definition part)

- Authentication of the herbs (as above)
- Keeping herbarium specimen for comparison and identification
- Assay of the liquid/dry extract is required considering at least one marker compound

  Assay procedure includes any of the following:

  - Trimetric procedure (where ever possible)
  - Spectro-photometric evaluation e.g. UV, IR etc
  - Chromatographic evaluation. e.g. TLC, HPTLC, HPLC, GC etc.
- Microbilogical assay
  - Total viable load (as described in BP or other official monographs or WHO guidelines enclosed in appendix)
  - Presence of pathogenic organisms (as described in BP or other official monographs or WHO guidelines enclosed in appendix)
- Safety assay -
  - Assay for the presences of Heavy metals e.g. Arsenic, Lead, Cadmium, Mercury and Copper
  - Assay for the presences of pesticides
  - (WHO guidelines enclosed in appendix)

Test	**Specification**
Appearance	Qualitative evaluation of the plant source, parts used, and its condition; e.g. whole plant, bark, leaves, dry or green in reduced, powdered or cut form etc.
Characteristics	May be evaluated according to its organoleptic characteristic
Moisture content	Should be specific according to the type of plant or plant material/part.
Identification/assay	Macroscopic: Must comply with the standard specifications. Microscopic: Must comply with the standard specifications. UV Spectroscopy: comply with the absorption bands test after extraction . Chromatographic: TLC, HPTLC, HPLC , Densitometry evaluation through evaluation of a values or retention time of the reference and test sample; comparison with the fingerprint of test and reference
Foreign matter	Must comply with the standard specifications.
Total Ash	Must comply with the standard specifications.
Acid insoluble ash	Must comply with the standard specifications.
Water soluble material	Must comply with the standard specifications.
Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil
Microbial contamination test	Total aerobic microbial count: Not more than 10^7 CFU/g or CFU/ml Total combined yeast and mold count: Not more than 10^5 CFU/g or CFU/ml *Escherichia coli:* Not more than 10^3 CFU/g or CFU/ml *Salmonella:* Nil (1g or 1ml) *Staphylococcus aureus*: Nil (1g or 1ml) *Clostridia*: Nil (1g or 1ml) *Pseudomonas:* Nil Should follow specifications of standard monograph
Aflatoxins/Mycotoxins	Should follow standard monograph (BP/USP/WHO/EMA guidelines); i.e. Aflatoxin B1: Not more than 2μg/kg, Sum of Aflatoxins B1, B2, G1, G2): not more than 4ppb.
Pesticide Residues	Must comply with the standards recommended by standard monograph (USP/WHO/EMA guidelines).
Assay	Quantitative measure of the marker compound(s) in the test sample in comparison to reference compound(s).

3. Finished herbal products or herbal medicinal products (considered E in definition part)

The finished herbal products may be of following types –

a. Solid: Powder (Dusting, Effervescent/non-effervescent), tablet (Coated/non-coated), capsule (Hard/soft gelatin, HPMC coated/non-coated/gastro-resistant)
b. Liquid: Syrup, Suspension, Emulsion, Elixir, Solution
c. Semisolid: Cream, Ointment
d. Suppository: Considered for the future
e. Injectables: Considered for the future

Solid

Powdered raw materials:

Test	**Specification**
Appearance	Qualitative evaluation of the powdered raw material considering color, odor, particle size etc. (macroscopic); Taxonomical test can take place where required.
Characteristics	May be evaluated according to its organoleptic characteristics
Foreign matters	Must comply with the standard specifications
Total Ash	Must comply with the standard specifications
Acid insoluble Ash	Must comply with the standard specifications
Water soluble materials	Must comply with the standard specifications
Moisture content	Should be specific according to the type of plant or plant material/part
Identification/assay	Macroscopic Microscopic UV Spectroscopy: comply with the absorption bands test with the reference. Chromatographic: TLC, HPTLC, HPLC, Densitometric evaluation through evaluation of a values or retention time of the reference and test sample; comparison with the fingerprint of test and Reference.
Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil

Microbial contamination test	Total aerobic microbial count: Not more than 10^7 CFU/g or CFU/ml Total combined yeast and mold count: Not more than 10^5 CFU/g or CFU/ml *Escherichia coli:* Not more than 10^3 CFU/g or CFU/ml *Salmonella:* Nil (1g or 1ml) *Staphylococcus aureus*: Nil (1g or 1ml) *Clostridia*: Nil (1g or 1ml) *Pseudomonas:* Nil Should follow specifications of standard monograph
Aflatoxins/ Mycotoxins	Should follow standard monograph (BP/USP/WHO/EMA guidelines); i.e. Aflatoxin B1: Not more than 2µg/kg, Sum of Aflatoxins B1, B2, G1, G2): not more than 4ppb.
Pesticide residues	Must comply with the standard recommended by standard monograph (USP/WHO/EMA guidelines)
Assay	Quantitative measure of the marker compound(s) in the test sample in comparison to reference compound(s).

Dusting power/effervescent powder in sachet:

Test	**Specification**
Appearance	Qualitative evaluation of the powdered raw material considering color, odor, taste particle size etc. (macroscopic). Taxonomical test can take place where required.
Characteristics	May be evaluated according to its organoleptic characteristics
Average net content Uniformity of filling weight	Must comply with the standard specifications.
Moisture content	Should specific according to the type of plant or plant material/part.
Identification/assay	Macroscopic Microscopic UV Spectroscopy: comply with the absorption bands test with the reference. Chromatographic: TLC, HPTLC, HPLC, Densitometric evaluation through evaluation of a values or retention time of the reference and test sample; comparison with the fingerprint of test and Reference.
Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil

Microbial contamination test	Total aerobic microbial count: Not more than 10^7 CFU/g or CFU/ml Total combined yeast and mold count: Not more than 10^5 CFU/g or CFU/ml *Escherichia coli:* Not more than 10^3 CFU/g or CFU/ml *Salmonella:* Nil (1g or 1ml) *Staphylococcus aureus*: Nil (1g or 1ml) *Clostridia*: Nil (1g or 1ml) *Pseudomonas:* Nil Should follow specifications of standard monograph
Aflatoxins/Mycotoxins	Should follow standard monograph (BP/USP/WHO/EMA guidelines); i.e. Aflatoxin B1: Not more than 2μg/kg, Sum of Aflatoxins B1, B2, G1, G2): not more than 4ppb.
Pesticide Residues	Must comply with the standard recommended by standard monograph (USP/WHO/EMA guidelines)
Assay	Quantitative measure of the marker compound(s) in the test sample in comparison to reference compound(s).

Tablet

Test	**Specification**
Appearance	Size & Shape: Round, oval, oblong etc. Color: as defined
Average weight and Uniformity of weight	Average weight per tablet within considerable weight variation limit and uniformity must comply with the standard specifications as per monograph (consider BP/USP).
Hardness	Must comply as per the set specifications.
Thickness	Must comply as per the set specifications.
Friability	Must comply as per the set specification/monograph
Moisture content	Must comply as per the set specification.
Disintegration	Test of disintegration as per the set specification
Dissolution rate	Must comply as per the set specification/monograph
Identification/assay	Tritrimetric: when identification & assay is possible through tritration. UV Spectroscopy: comply with the absorption bands test with the reference Chromatographic: TLC, HPTLC, HPLC, Densitometric evaluation through evaluation of a values or retention time of the reference and test sample; comparison with the fingerprint region of test and reference
Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil

Microbial contamination test	Total aerobic microbial count: Not more than 10^7 CFU/g or CFU/ml Total combined yeast and mold count: Not more than 10^5 CFU/g or CFU/ml *Escherichia coli:* Not more than 10^3 CFU/g or CFU/ml *Salmonella:* Nil (1g or 1ml) *Staphylococcus aureus*: Nil (1g or 1ml) *Clostridia*: Nil (1g or 1ml) *Pseudomonas:* Nil Should follow specifications of standard monograph.
Aflatoxins/Mycotoxins	Should follow standard monograph (BP/USP/WHO/EMA guidelines); i.e. Aflatoxin B1: Not more than 2μg/kg, Sum of Aflatoxins B1, B2, G1, G2): not more than 4ppb.
Pesticide Residues	Must comply with the standard recommended by standard monograph (USP/WHO/EMA guidelines).

Capsule

Test	**Specification**
Appearance & Material of shell	Size: 0, 00, 01, 02 etc, Color of the capsule shell: as defined Shell: Hard Gelatin/ soft gelatin/ HPMC etc.
Average weight and uniformity of weight	Average weight per capsule should comply with the standard specification of monograph (BP/USP). Uniformity of filled weight should also be within the range as per the standard monograph.
Disintegration time	Must comply with the standard specification of monograph
Dissolution	Must comply as per the set specification/monograph
Microbial Contamination test	Total aerobic microbial count: Not more than 10^7 CFU/g or CFU/ml Total combined yeast and mold count: Not more than 10^5 CFU/g or CFU/ml *Escherichia coli:* Not more than 10^3 CFU/g or CFU/ml *Salmonella:* Nil (1g or 1ml) *Staphylococcus aureus*: Nil (1g or 1ml) *Clostridia*: Nil (1g or 1ml) *Pseudomonas:* Nil Should follow specifications of standard monograph.
Identification/assay	Tritrimetric: when identification & assay is possible through tritration. UV Spectroscopy: comply with the absorption bands test with the reference. Chromatographic: TLC, HPTLC, HPLC, Densitometric evaluation through evaluation of R_f values or retention time of the reference and test sample; comparison with the fingerprint of test and reference

Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil
Pesticide Residues	Should follow standard monograph (WHO/EMA guidelines)

Liquid

Test	**Specification**
Appearance	Color: As per defined Odor: As per defined
Average filled volume	Must comply with the specification as claimed
pH	Test of pH as per the set specifications
Weight per ml	Weight per ml as per the set specifications
Viscosity	Test of viscosity as per the set specifications
Microbial contamination test	Total aerobic microbial count: Not more than 10^7 CFU/g or CFU/ml Total combined yeast and mold count: Not more than 10^5 CFU/g or CFU/ml *Escherichia coli:* Not more than 10^3 CFU/g or CFU/ml *Salmonella:* Nil (1g or 1ml) *Staphylococcus aureus*: Nil (1g or 1ml) *Clostridia*: Nil (1g or 1ml) *Pseudomonas:* Nil Should follow specifications of standard monograph.
Content of antimicrobial agent	Test for the concentration of antimicrobial agent to identify the limit as per the specification.
Identification/assay	Tritrimetric: when identification & assay is possible through tritration. UV Spectroscopy: comply with the absorption bands test with the reference. Chromatographic: TLC, HPTLC, HPLC, Densitometric evaluation through evaluation of R_f values or retention time of the reference and test sample; comparison with the fingerprint of test and reference

Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil
Pesticide Residues	Should follow standard monograph (WHO/EMA guidelines)

Semisolid

Test	**Specification**
Appearance	Color: As per defined Odor: As per defined
pH	Test of pH as per the set specifications
Weight per ml	Weight per ml as per the set specifications
Viscosity	Test of viscosity as per the set specifications
Microbial contamination test	Should follow specifications of standard monograph
Content of antimicrobial agent	Test for the concentration of antimicrobial agent to identify the limit as per the specification.
Identification/assay	Tritrimetric: when identification & assay is possible through tritration. UV Spectroscopy: comply with the absorption bands test with the reference Chromatographic: TLC, HPTLC, HPLC, Densitometric evaluation through evaluation of R_f values or retention time of the reference and test sample; comparison with the fingerprint of test and reference
Heavy metals	Arsenic: 5ppm Lead: 10ppm Cadmium: 0.3ppm Mercury: Nil Copper: Nil
Pesticide Residues	Should follow standard monograph (WHO/EMA guidelines)

Conclusion

During setting the standardization and quality control parameter every manufacturer should have their specification, criteria and standard SOP commensurate with the official pharmacopoeias, WHO or other standard guidelines, because for herbal materials the standardization and test criteria will totally depend on the raw material that the company uses. For example, to manufacture ginseng capsule a company can use material having 20% ginsenoside where as other company can use 35%. So, both the company has to set their own quality control and standardization test criteria depending on the material they are using. But most important thing is that, the procedure should be validated.

To set the standard criteria, WHO, EMA, German Commission E etc have formulated excellent procedures and guidelines. If we can follow those guidelines, we can easily take our products to world standard.

For the development of the herbal/ alternative systems of medicines collaborative efforts must be established between the industries and academia/ research institutions.

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