

Annex 3A

VOLUNTARY CERTIFICATION SCHEME FOR AYUSH
PRODUCTS Certification Criteria
SECTION III

GMP Requirements Based On WHO Guidelines for
AYUSH Premium Mark

1.Introduction

The increasing use of herbal medicines and the growing demand of the global market for such products has raised concerns on the quality and safety of herbal materials and finished herbal products with the respective national health authorities. Although traditional systems of medicine have been recognized and accepted in most countries, efforts to provide validated techniques to ensure the quality, safety and efficacy of products have gained importance only in recent times. The quality of the finished herbal products is largely dependent and influenced by the quality of the raw materials used. Because herbal ingredients are of complex and variable nature, the requirements and methods for quality control of finished products specially for combination product poses an additional challenge. Therefore, controls of raw material, storage and processing assume particular importance in the manufacturing process of herbal medicinal product.

Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicines are prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources. As a result, it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products. Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/or plant parts and the number and small quantity of defined active ingredients, the production and primary processing have a direct influence on the quality of herbal medicines. For this reason, the application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.

2.Scope

This standard prescribes the product requirements, good manufacturing practices, requirements for competence of personnel and testing of AYUSH Products included in the API /Unani Pharmacopoeia / Siddha Pharmacopoeia / Homeopathic Pharmacopoeia, Herbal Generics in approved books and Herbal P&P

3.Terminology

- a) **AYUSH Products** – products of Ayurveda, Unani, Siddha and Homeopathy systems of medicine that are covered under the Drugs and Cosmetics Act, Herbal Generics in approved books and Herbal P&P.
- b) **Acceptance criteria:** Numerical limits, ranges, or other suitable measures for acceptance of the herbal substance, preparation and medicines based on the results of analytical procedures.
- c) **Authorized Person-** A permanent full-time employee of the organization who has been trained and has defined responsibility to conduct the relevant / activity process.
- d) **Constituents with known therapeutic activity:** are chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.
- e) **Drug extract ratio (DER):** means the ratio between the quantity of herbal substance used in the manufacture of a herbal preparation and the quantity of the herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.
- f) **Extraction solvents:** are solvents which are used for the extraction process.
- g) **Genuine (Native) herbal preparation:** refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.

- h) **Ratio of herbal substance to genuine herbal preparation (DER genuine):** is the ratio of the quantity of the herbal substance to the quantity of the resulting genuine herbal preparation. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the genuine herbal preparation obtained.
- i) **Herbal medicinal products:** any medicinal product, exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.
- j) **Herbal preparations:** are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.
- k) **Herbal substances:** all mainly whole, fragmented or cut plants, plant parts, algae, fungi, and lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety).
- l) **Herbal teas:** consist exclusively of one or more herbal substance(s) intended for oral aqueous preparations through decoction, infusion or maceration. The preparation is prepared immediately before use. Herbal teas are usually supplied in bulk form or in sachets.
- m) **Markers:** are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or an herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the Herbal Medicinal Product if the marker has been quantitatively determined in the herbal substance or herbal preparations.

There are two categories of markers:

- **Active markers:** are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.
 - **Analytical marker:** are constituents or groups of constituents that serve for analytical purposes.
- n) **Quantification:** means adjusting the herbal preparation to a defined range of constituents exclusively achieved by blending different batches of herbal substances and/or herbal preparations (e.g. quantified extracts).
 - o) **Solvent:** An inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a herbal preparation or the manufacture of a herbal medicinal product.
 - p) **Specification:** A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal preparation / herbal substance or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal preparation / herbal substance and/or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.
 - q) **Standardization:** means adjusting the herbal substance / herbal preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardized extracts).
 - r) **Active ingredients** -The herbal substance (s) or the herbal preparation(s) will be considered to be active ingredient(s) of a herbal medicine(s). However, if constituents with known therapeutic activities are known, the active ingredients should be standardized to contain a defined amount of this/these constituent(s).
 - s) **Blending** -Blending is the process of combining materials or different batches to produce a homogeneous intermediate or finished product.
 - t) **Medicinal plant** -Medicinal plants are plants (wild or cultivated) used for medicinal purposes.
 - u) **Medicinal plant materials – see herbal substances**
 - v) **Therapeutic activity** - Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses, improvement of symptoms of illnesses, as well as

beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being.

4. Requirements

- 4.1** The AYUSH products shall be processed from suitable quality raw materials as per the method of production and composition defined in the API/ UP/SP/HP.
- 4.2** The raw materials used shall comply with the requirements for raw materials specified in the API/UP/SP/HP.
- 4.3** The finished AYUSH products shall comply with
 - a) The requirements specified in API /UP/SP/HP.
- 4.4** AYUSH products shall be processed, handled, and packaged under hygienic conditions adhering to the Good Manufacturing Practices detailed below;

4.4.1 Personal hygiene

- a) All personnel deployed in an AYUSH product processing unit, before and during employment shall undergo health examinations at least once a year. Personnel conducting visual inspections shall also undergo periodic eye examinations.
- b) All personnel shall be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.
- c) Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle starting materials, packaging materials, in-process materials or drug products until the condition is no longer judged to be a risk.
- d) All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.
- e) Direct contact shall be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.
- f) To ensure protection of the product from contamination, personnel shall wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, shall be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.
- g) Smoking is not permitted on the premises (except in designated areas). Eating, drinking, chewing, and keeping plants, food, drink, personal medicines, incense sticks, garlands etc. shall not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.
- h) Personal hygiene procedures including the use of protective clothing shall apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g. contractors' employees, visitors, senior managers, and inspectors.

4.4.2 Premises

- a) Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.
- b) The layout and design of premises shall be such that it minimizes the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- c) Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures shall be taken to avoid cross-contamination and facilitate cleaning.
- d) Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents a minimum risk of causing any contamination of materials or products.
- e) Premises used for the manufacture of finished products shall be suitably designed and constructed to facilitate good sanitation.
- f) Premises shall be carefully maintained, and it shall be ensured that repair and maintenance operations do not present any hazard to the quality of products.

- g) Premises shall be cleaned and, where applicable disinfected. -
- h) Electrical supply, lighting, temperature, humidity and ventilation shall be appropriate and such that they do not adversely affect, directly or indirectly, either the AYUSH products during their manufacture and storage or the accurate functioning of equipment.
- i) Premises should be designed and equipped to afford maximum protection against the entry of insects, birds or other animals. There shall be a procedure for rodent and pest control.
- j) Premises shall be designed to ensure the logical flow of materials and personnel

4.4.2.1 Ancillary areas

- a) Rest and refreshment rooms shall be separate from manufacturing and control areas.
- b) Facilities for changing and storing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the number of users. Toilets shall not have direct access to the production or storage areas and may preferably be located away from these areas.
- c) Maintenance workshops, should if possible, be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- d) Animal houses should be well isolated from other areas, with separate entrances (animal access) and air-handling facilities.

4.4.2.2 Storage areas

- a) Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.
- b) Storage areas should be designed or adapted to ensure good storage conditions. In particular, they shall be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these shall be provided, controlled, monitored and recorded where appropriate.
- c) Receiving and dispatch bays shall be separated and materials and products be protected from the weather. Receiving areas shall be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.
- d) Where quarantine status is ensured by storage in separate areas, these areas shall be marked and their access restricted to authorized personnel. Any system replacing the physical quarantine shall ensure equivalent security.
- e) Segregation areas shall be provided for the storage of rejected, recalled, or returned materials or products and clearly identified.
- f) Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.
- g) Printed packaging materials are considered critical to indicate the conformity of the pharmaceutical product by its labelling and special attention shall be paid to sampling and the safe and secure storage of these materials.
- h) There should normally be a separate sampling area for starting materials.
- i) If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

4.4.2.3 Weighing areas

- a) The weighing of starting materials and the estimation of yield by weighing shall be carried out in separate weighing areas designed for that use, for example with provisions for dust control. Such areas may be part of either storage or production areas.

4.4.2.4 Production areas

- a) Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

- b) The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different AYUSH products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.
- c) Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks and open joints, shall not shed particulate matter, and shall permit easy and effective cleaning and, if necessary, disinfection.
- d) Pipework, light fittings, ventilation points and other services shall be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- e) Drains should be of adequate size and designed and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they shall be shallow to facilitate cleaning and disinfection.
- f) Production areas shall be effectively ventilated, with air control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment.
- g) Premises for the packaging of AYUSH products shall be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- h) Production areas shall be well lit, particularly where visual on-line controls are carried out.

4.4.2.5 Quality Control Areas

- a) The organization shall have in-house testing facilities / Quality control laboratories and these shall be separated from production areas. Areas where biological, or microbiological test methods are employed, shall be separated from each other and other laboratories.
- b) Quality control laboratories shall be designed to suit the operations to be carried out in them. Sufficient space shall be given to avoid mix-ups and cross-contamination of samples and reagents. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.
- c) The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There shall be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, and microbiological laboratories.
- d) A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

4.4.3 Equipment

- a) Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment shall aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- b) Equipment shall be installed, cleaned, maintained and operated in such a way as to minimize any risk of error or contamination.
- c) Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- d) All service piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.
- e) Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.
- f) Production equipment should be thoroughly cleaned on a scheduled basis.
- g) Laboratory equipment and instruments shall be suited to the testing procedures undertaken.
- h) Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.

- i) Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product shall not be reactive, additive, or absorptive to an extent that would affect the quality of the product. Justification that equipment will not contaminate the product shall be provided by the manufacturer. Non-wooden equipment should be used unless tradition demands wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.), this should be dedicated, unless otherwise justified. When such equipment is used, it is advisable that it does not come into direct contact with chemicals or contaminated material. If the use of wooden equipment is unavoidable, special consideration must be given to its cleaning as wooden materials may retain odors, be easily discolored and are easily contaminated.
- j) Defective equipment shall be removed from production and quality control areas. If this is not possible, it shall be clearly labelled as defective to prevent use.
- k) Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions shall be taken to minimize contamination.
- l) Non-dedicated equipment shall be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.
- m) Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment should be dried immediately after cleaning to prevent the growth of microorganisms. Cleaning with compressed air and brushes should be used with care and avoided if possible, as these methods increase the risk of product contamination.
- n) Current drawings of critical equipment and support systems should be maintained

4.4.4 Materials

- a) No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the starting material, packing material, work in process or finished product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.
- b) All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.
- c) All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-in, first-out rule.
- d) Water used in the manufacture of pharmaceutical products shall comply with WHO guidelines for drinking (potable) water quality.

4.4.4.1 Starting materials

- a) Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. The specifications established by the manufacturer for the starting materials should be discussed with the supplier. All incoming materials should be checked to ensure that the consignment
- b) corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.
- c) Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.
- d) If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- e) Starting materials in the storage area should be appropriately labelled.
- f) Only starting materials released by the quality control department and within their shelf-life shall be used. Reference to WHO guidelines on stability studies for herbal materials or herbal preparations should be made.
- g) Materials dispensed for each batch of the final product shall be kept together and conspicuously labelled as such.

4.4.4.2 Labels shall bear at least the following information:

- a) the designated name of the product and the internal code reference where applicable;
- b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
- c) the status of the contents (e.g. in quarantine, on test, released, rejected, returned, recalled);
- d) where appropriate, an expiry date or a date beyond which retesting is necessary.
- e) analytical Report no. on label of approved material
- f) no. of container upon total no. of containers.

4.4.4.3 Packaging materials

- a) The purchase, handling and control of primary and printed packaging materials should be as for starting materials.
- b) Printed packaging materials shall be stored in secure conditions to exclude the possibility of unauthorized access. Roll-feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.
- c) Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.
- d) Outdated or obsolete primary packaging material or printed packaging material shall be destroyed and its disposal recorded.
- e) All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

4.4.4.4 Intermediate and bulk products

- a) Intermediate and bulk products should be kept under appropriate conditions.
- b) Intermediate and bulk products purchased as such shall be handled on receipt as though
- c) they were starting materials.

4.4.4.5 Finished products

- a) Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

4.4.4.6 Rejected, recovered, reprocessed and reworked materials

- a) Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner.
- b) Whatever action is taken should be approved by authorized personnel and recorded.
- c) The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record shall be kept of the reworking or recovery. A reworked batch shall be given a new batch number.
- d) The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture shall be authorized beforehand. This recovery shall be carried out after evaluation of the risks involved, including any possible effect on shelf-life. The recovery shall be recorded.
- e) Any finished product that has been reprocessed reworked or into which a recovered product has been incorporated, shall be retested for all requirements.

4.4.4.7 Recalled products

- a) Recalled products shall be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

4.4.4.8 Returned goods

- a) Products returned from the market shall be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabeling, or alternative action taken only after they have been critically assessed. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it shall not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

4.4.4.9 Waste materials

- a) Toxic substances and flammable materials shall be stored in suitably designed, separate, enclosures, as required by national legislation.
- b) Waste material shall not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals. Waste material shall be disposed of as required by national legislation.

4.4.4.10 Miscellaneous

- a) Rodenticides, insecticides, fumigating agents and sanitizing materials shall not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

4.4.4.11 Reference samples and standards - The reference standard for a herbal medicine may be a botanical sample of the herbal material; a sample of the herbal preparation, e.g. extract; or a chemically defined substance, e.g. a known active constituent, a marker substance or a known impurity. The reference standard should be of a quality appropriate to its purpose. If the herbal medicine is not described in a recognized pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the medicinal plant (e.g. if the whole medicinal plant is a tree) should be available. All reference standards should be stored under appropriate conditions to prevent degradation. Their expiry and/or revalidation date should be determined and indicated.

4.4.5 Documentation

- a) Documents should be approved, signed and dated by the appropriate responsible
- b) persons. No document should be changed without authorization and approval.
- c) Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. Reproduced documents should be clear and legible.
- d) Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.
- e) Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of the AYUSH products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

4.4.5.1 Labels

- a) Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format.
- b) For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

4.4.5.2 Packaging instructions

- a) Packaging instructions for each product, pack size and type shall be defined. These should include, or make reference to:

- i. the name of the product;
- ii. a description of its pharmaceutical form, strength and directions for use;
- iii. the pack size expressed in terms of the number, weight or volume of the product in the final container;
- iv. a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
- v. where appropriate an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- vi. special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
- vii. a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- viii. details of in-process controls with instructions for sampling and acceptance limits.

4.4.5.3 Batch processing records

- a) A batch processing record shall be kept for each batch processed. It shall be based on the relevant parts of the currently approved specifications on the record.
- b) Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.
- c) During processing, the following information shall be recorded at the time each action is taken, and after completion the record shall be dated and signed by the person responsible for the processing operations;
 - i. the name of the product;
 - ii. the number of the batch being manufactured;
 - iii. dates and times of commencement, of significant intermediate stages, and of completion of production;
 - iv. the name of the person responsible for each stage of production;
 - v. the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
 - vi. the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount or any recovered or reprocessed material added);
 - vii. any relevant processing operation or event and the major equipment used;
 - viii. the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
 - ix. the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
 - x. notes on special problems including details, with signed authorization for any deviation from the master formula.

4.4.5.4 Batch packaging records

- a) A batch packaging record shall be kept for each batch or part batch processed.
- b) Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.
- c) The following information shall be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

- i. the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
- ii. the date(s) and time(s) of the packaging operations;
- iii. the name of the responsible person carrying out the packaging operation;
- iv. the initials of the operators of the different significant steps;
- v. the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- vi. details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
- vii. whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
- viii. notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
- ix. the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

4.4.5.5 Standard operating procedures (SOPs) and records

- a) Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:
 - i. equipment assembly and validation;
 - ii. analytical apparatus and calibration;
 - iii. maintenance, cleaning and sanitization;
 - iv. personnel matters including qualification, training, clothing and hygiene;
 - v. environmental monitoring;
 - vi. pest control;
 - vii. complaints;
 - ix. recalls
 - x. returns
 - xi. reprocessing of a batch
 - xii. handling of hazardous materials like cleaning liquids, pesticides, disinfectants, gases, flammable materials, solvents etc
 - xiii. entry into and exit from production areas
 - xiv. preparation, handling, using standardization and frequency of retesting of reagents
 - xv. handling of materials with out-of-specification results of analysis
- b) There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.
- c) The records of the receipts should include:
 - i. the name of the material on the delivery note and the containers;
 - ii. the "in-house" name and/or code of material if different from (a);
 - iii. the date of receipt;
 - iv. the supplier's name and, if possible, manufacturer's name;
 - v. the manufacturer's batch or reference number
 - vi. the total quantity, and number of containers received;
 - vii. the batch number assigned after receipt;
 - viii. any relevant comment (e.g. state of the containers).

- d) There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.
- e) Standard operating procedures should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.
- f) There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.
- g) The sampling instructions should include:
 - i. the method of sampling and the sampling plan;
 - ii. the equipment to be used;
 - iii. any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
 - iv. the amount(s) of sample(s) to be taken;
 - v. instructions for any required subdivision of the sample;
 - vi. the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
 - vii. any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.
- h) There shall be a standard operating procedure describing the details of the unique batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number. The batch numbering applied to the processing stage and to the respective packaging stage should be related to each other.
- i) Batch-number allocation shall be recorded, with details of at least the date of allocation, product identity and size of batch.
- j) There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.
- k) Analysis records shall include at least the following data:
 - i. the name of the material or product and, where applicable, dosage form;
 - ii. the batch number and, where appropriate, the manufacturer and/or supplier;
 - iii. references to the relevant specifications and testing procedures;
 - iv. test results, including observations and calculations, and reference to any specifications (limits);
 - v. date(s) and reference number(s) of testing;
 - vi. the initials of the persons who performed the testing;
 - vii. the date and initials of the persons who verified the testing and the calculations, where appropriate;
 - viii. a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
- l) Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.
- m) Records shall be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.
- n) Records shall be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.
- o) The use of all equipment and the areas where products have been processed should be appropriately recorded in chronological order.
- p) There shall be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned, and these shall be followed.

4.4.6 Good practices in production

- a) All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution shall be carried out under good hygienic and good manufacturing practices.
- b) Checks on yields and reconciliation of quantities shall be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- c) Operations on different products shall not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.
- d) At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number.
- e) Access to production premises shall be restricted to authorized personnel.

4.4.6.1 Prevention of cross-contamination and bacterial contamination during production

- a) When dry materials and products are used in production, special precautions shall be taken to prevent the generation and dissemination of dust. Provision shall be made for proper air control (e.g. supply and extraction of air of suitable quality).
- b) Contamination of a starting material or of a product by another material or product shall be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc.
- c) Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:
 - i. carrying out production in dedicated and self-contained areas,
 - ii. conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
 - iii. providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
 - iv. minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
 - v. wearing protective clothing where products or materials are handled;
 - vi. using cleaning and decontamination procedures of known effectiveness;
 - vii. using a "closed system" in production;
 - viii. testing for residues;
 - ix. using cleanliness status labels on equipment.
- d) Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.
- e) Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

4.4.6.2 Processing operations

- a) Before any processing operation is started, steps shall be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.
- b) Defective equipment shall be withdrawn from use and appropriately labelled and preferably covered until the defect has been rectified. After use, production equipment shall be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.
- c) Time limits for storage of equipment after cleaning and before use should be stated, be based on data and scheduled by the manufacturer. Containers for filling shall be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.
- d) Any significant deviation from the expected yield should be recorded and investigated.

- e) Measuring, weighing, recording, and control equipment and instruments shall be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked at appropriate intervals or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due shall be clearly indicated, preferably on a label attached to the instrument.
- f) Repair and maintenance operations should not present any hazard to the quality of the products.

4.4.6.3 Packaging operations

- a) Different products shall not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.
- b) Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation.
- c) The name and batch number of the product being handled shall be displayed at each packaging station or line.
- d) Normally, filling and sealing shall be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.
- e) The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging shall be checked and recorded. Printing by hand, should be rechecked at regular intervals.
- f) Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.
- g) Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- h) Regular on-line control of the product during packaging shall include at least checks on:
 - i. the general appearance of the packages;
 - ii. whether the packages are complete;
 - iii. whether the correct products and packaging materials are used;
 - iv. whether any overprinting is correct;
 - v. the correct functioning of line monitors.
- i) Samples taken away from the packaging line shall not be returned.
- j) Products that have been involved in an unusual event during packaging shall be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record shall be kept of this operation.
- k) Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated, satisfactorily accounted for, and recorded before release.
- l) Upon completion of a packaging operation, any unused batch-coded packaging materials shall be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

4.4.7 Good practices in quality control

- a) Quality control is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

- b) The quality control function should have adequate resources available so as to ensure that all the quality control arrangements are effectively and reliably carried out., which includes;
 - i. sampling of starting materials, packaging materials, intermediate products, bulk products and finished products by approved methods ;
 - ii. performance of qualification and validation;
 - iii. recording for demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
 - iv. the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the relevant regulatory requirements; the ingredients shall be of the required purity, in their proper container and correctly labelled;
 - v. records shall be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;
 - vi. no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the relevant regulatory requirement.
 - vii. sufficient samples of starting materials and products shall be retained to permit future examination of the product if necessary; the retained product shall be kept in its final pack unless the pack is exceptionally large.
- c) Assessment of finished products includes checking the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

4.4.7.1 Control of starting materials and intermediate, bulk and finished products

- a) All tests shall follow the instructions given in the relevant written test procedure for each material or product as specified in the API or the importing country Regulation. The result should be checked by the supervisor before the material or product is released or rejected.
- b) Samples shall be representative of the batches of material from which they are taken in accordance with the approved written procedure.
- c) Sampling shall be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling. Samples drawn for checking/testing shall not be released for sale.
- d) Sampling equipment shall be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.
- e) Each sample container should bear a label indicating:
 - i. the name of the sampled material;
 - ii. the batch or lot number;
 - iii. the number of the container from which the sample has been taken;
 - iv. the number of the sample;
 - v. the signature of the person who has taken the sample;
 - vi. the date of sampling.
- f) Out-of-specification results obtained during testing of materials or products shall be investigated in accordance with an approved procedure. Records should be maintained.

4.4.7.2 Test requirements - Starting and packaging materials

- a) Before releasing a starting or packaging material for use, they shall be tested for conformity with specifications for identity, strength, purity and other quality parameters.
- b) In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities.

4.4.7.3 Test requirements - In-process control

- a) In-process control records should be maintained and form a part of the batch records.

4.4.7.4 Test requirements - Finished products

- a) For each batch of AYUSH product, there shall be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.
- b) Products failing to meet the established specifications or any other relevant quality criteria shall be rejected.

4.4.7.5 Batch record review

- a) Production and quality control records shall be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications shall be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and should include the conclusion and follow-up action.
- b) Retention samples from each batch of finished product shall be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. Samples of active starting materials shall be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) shall be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

4.4.7.6 Stability studies

- a) The quality and stability of finished AYUSH products and, when necessary, of starting materials and intermediate products shall be evaluated.
- b) Expiry dates and shelf-life specifications shall be established on the basis of stability tests related to storage conditions.
- c) A written programme for on-going stability determination should be developed and implemented to include elements such as:
 - i. a complete description of the AYUSH product involved in the study;
 - ii. the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
 - iii. provision for the inclusion of a sufficient number of batches;
 - iv. the testing schedule for each AYUSH product;
 - v. provision for special storage conditions;
 - vi. provision for adequate sample retention;
 - vii. a summary of all the data generated, including the evaluation and the conclusions of the study.
- d) Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

4.4.8 Qualification and validation

- a) The company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.
- b) The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.
- c) Qualification and validation should establish and provide documentary evidence that:
 - i. the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP;

- ii. the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications ;
 - iii. the premises, supporting utilities and equipment operate in accordance with their design specifications
 - iv. a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.
- d) Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.
 - e) The ongoing programme should follow their first implementation and should be based on an annual review. On review any changes to the initial programme to be justified.
 - f) The responsibility of performing validation should be clearly defined.
 - g) Validation studies should be conducted in accordance with predefined and approved protocols.
 - h) A written report summarizing the results recorded and the conclusions reached should be prepared and stored.
 - i) Processes and procedures should be established on the basis of the results of the validation performed.

4.4.9. Complaints

- a) All complaints including those of adverse side effects and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.
- b) The person responsible for handling complaints and deciding on the measures to be taken to deal with them shall have appropriate training and/or experience in the specific features of the quality control of herbal medicines.
- c) There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- d) Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for quality control shall be involved in the review of such investigations.
- e) If a product defect is discovered or suspected in a batch, other batches that may contain reprocessed product from the defective batch should also be investigated.
- f) Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- g) All decisions made and measures taken as a result of a complaint shall be recorded and referenced to the corresponding batch records.
- h) Complaints records shall be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.
- i) The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, counterfeiting or any other serious quality problems with a product.

4.4.10 Product recalls

- a) There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.
- b) The authorized person should be responsible for the execution and coordination of recalls.
- c) There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.
- d) Recalled products shall be stored in a secure segregated area while their fate is decided.
- e) All customers / competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.
- f) The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers

(including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

- g) The progress of the recall process should be monitored and recorded.
- h) Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.
- i) The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

4.4.11 Personnel

- a) The organization structure and the responsibilities and authorities of personnel shall be defined. The manufacturer shall have adequate number of personnel with the necessary qualifications and practical experience. Individual responsibilities and authorities should be clearly defined and understood by the persons concerned and recorded as written descriptions.
- b) There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP.
- c) All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.
- d) Key personnel responsible for supervising the manufacture and quality control of AYUSH products shall possess the qualifications of (a) an expert in Ayurveda /Unani /Siddha /Homeopathy (b) Chemist who shall possess at least a Bachelor's Degree in Science, Pharmacy or Pharmacy (Ayurveda/ Siddha/ Unani/ Homeopathy) (c) Botanist who shall possess at least a Bachelor's degree in Science(Medicine) or Pharmacy or Pharmacy (Ayurveda / Siddha / Unani / Homeopathy and adequate practical experience as required by national legislation in the Drugs and Cosmetics Act .
 - aa) The release of herbal medicines shall be authorized by a person (known as 'Responsible Person') who has been trained in the specific features of processing and quality control of herbal substances, herbal preparations and finished herbal products.
 - bb) Personnel dealing with the production and quality control of herbal medicines shall have adequate training in the specific issues relevant to herbal medicines.

4.4.12 Training

- a) The personnel should have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, photochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of herbal medicines).
- b) Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

5. Packing - The products shall be packed in clean, hygienic bottles/containers / made of materials suitable for the respective dosage form and confirmed with suitable stability studies as per regulations.

6. Labelling - The AYUSH products shall be marked legibly on the label of the bottle/package;

- a) Name of the AYUSH Product;
- b) List of active ingredients, showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
- c) Dosage form
- d) Batch number assigned by the manufacturer;
- e) the expiry date in an uncoded form;
- f) any special storage conditions or handling precautions that may be necessary;
- g) directions for use, and warnings and precautions that may be necessary;
- h) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.
- i) Any others as required by the Regulation

7. References

API
UNANI PH
SIDDHA PH
HOMEOPATHIC PH
Indian Pharma
WHO guidelines on good manufacturing practices (GMP) for herbal medicine