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African Traditional Medicine — Good manufacturing practices (GMP) for herbal medicines

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Foreword

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This African Standard was prepared by the ARSO Technical Harmonization Committee on Traditional African Medicine (ARSO/THC 13).

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Introduction

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 plant 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.

With the constant increase in the use of herbal medicines worldwide and the rapid expansion of the global market, the safety and quality of herbal materials and finished herbal products have become a major concern for health authorities, pharmaceutical industries and the public. The safety and efficacy of herbal medicines largely depend on their quality. Requirements and methods for quality control of finished herbal products, particularly for combining/mixing herbal products, are far more complex than for chemical drugs. The quality of finished herbal products is also influenced by the quality of the raw materials used.

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 has a direct influence on the quality of herbal medicines. The manufacturing process is one of the key steps where quality control is required to ensure quality of medicinal products, including herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality (WHO, 2007).

It is recognized that many of the traditional medicine manufacturers are in the categories of small and medium enterprises (SMEs) with fairly uncomplicated manufacturing facilities. These guidelines apply to SMEs in a proportionate nature which shall take into account the budgetary outlay and the need to avoid undue economic and administrative burden while ensuring that the safety, efficacy and quality of the herbal medicinal products is not compromised.

African Traditional Medicine — Good manufacturing practices (GMP) for herbal medicines

1 Scope

This African standard provides guidelines on good manufacturing practices aimed at ensuring the safety, efficacy and quality of herbal medicinal products for human consumption.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ARS 53, *General principles of food hygiene — Code of practice*

ARS 56, *Pre-packaged foods — Labelling*

CD-ARS 950-2013, *African Traditional Medicine — Glossary*

CODEX STAN 193, *Codex general standard for contaminants and toxins in food and feed*

ISO 6888-1, *Microbiology of food and animal feeding stuffs — Horizontal method for the enumeration of coagulase-positive staphylococci (Staphylococcus aureus and other species) — Part 1: Technique using Baird-Parker agar medium*

ISO 6888-2, *Microbiology of food and animal feeding stuffs — Horizontal method for the enumeration of coagulase-positive staphylococci (Staphylococcus aureus and other species) — Part 2: Technique using rabbit plasma fibrinogen agar medium*

ISO 6888-3, *Microbiology of food and animal feeding stuffs — Horizontal method for the enumeration of coagulase-positive staphylococci (Staphylococcus aureus and other species) — Part 3: Detection and MPN technique for low numbers*

ISO 7251, *Microbiology of food and animal feeding stuffs — Horizontal method for the detection and enumeration of presumptive Escherichia coli — Most probable number technique*

ISO 16050, *Foodstuffs — Determination of aflatoxin B_1, and the total content of aflatoxin B_1, B_2, G_1 and G_2 in cereals, nuts and derived products — High performance liquid chromatographic method*

ISO 21527-2, *Microbiology of food and animal feeding stuffs — Horizontal method for the enumeration of yeasts and moulds — Part 2: Colony count technique in products with water activity less than or equal to 0.95*

AOAC Official Method 2001.04, *Determination of Fumonisins B_1 and B_2 in corn and corn flakes — Liquid chromatography with immunoaffinity column cleanup*

3 Definitions and abbreviations

For the purpose of this standard definitions in DARS 950:2015 and the following definitions apply.

3.1
Medicinal product

any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or

administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis (EC: 2001)

3.2
Herbalist
a traditional medical practitioner whose specialization lies in the use of herbs to treat various ailments. He/she to be knowledgeable in the efficacy, safety, dosage, and compounding of herbs (KS 2235: 2010).

3.3
Herbal medicinal product
Any medicinal product, exclusively containing as active ingredients 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 (EC 2001)

NOTE Herbal medicinal products may include natural plant substances such as seeds, berries, roots, leaves, bark, or flowers presented as herbs, herbal materials, herbal preparations and finished herbal products (WHO: 2007).

3.4
Medicinal plant
a wild or cultivated plant used for medicinal purposes (KS 2235: 2010)

3.5
Herbs
A plant that is valued for flavour, scent, or other qualities. Herbs have a variety of uses including culinary and medicinal. General usage differs between culinary herbs and medicinal herbs. In medicinal herbs include crude materials which could be derived from lichen, algae, fungi or higher plants, such as leaves, flowers, fruit, fruiting bodies, seeds, stems, wood, bark, roots, rhizomes or other parts, which may be entire, fragmented or powdered (WHO, 2007).

3.6
Herbal substances
All mainly whole, fragmented or cut plants, plant parts, algae, fungi, 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 and author). (EC, 2001)

3.7
Herbal preparations
Preparations 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 (EC, 2001). They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials (WHO, 2007).

3.8
Finished herbal products
Consist of herbal preparations made from one or more herbs.
Note: If more than one herb is used, the term “mixture herbal product” can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished herbal products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal (WHO, 2007)

3.9
Quality
Degree to which a set of inherent characteristics fulfils requirements (ISO 9000, 2005)

NOTE 1 The term “quality” can be used with adjectives such as poor, good or excellent.

NOTE 2 "Inherent", as opposed to "assigned", means existing in something, especially as a permanent characteristic.

3.10
Contamination
undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport (KS 2235, 2010)

3.11
Cross-contamination
contamination of a starting material, intermediate product or finished product by another starting material or product during production (KS 2235, 2010)

3.12
Aromatic plant
a wild or cultivated plant that has a characteristic aroma, may be used for medicinal or cosmetic purposes (KS 2235, 2010)

3.13
Excipient
any constituent of a medicinal product other than the active substance and the packaging material (EC, 2001)

3.14
Markers
chemically defined constituents of a herbal material utilized for control purposes. They may or may not contribute to the clinical efficacy. When they contribute to the clinical efficacy, however, evidence that they are solely responsible for the clinical efficacy may or may not be available. Markers are generally employed when constituents of known therapeutic activity are not known or are not clearly identified, and may be used to identify the herbal material or preparation or calculate their quantity in the finished product (WHO, 2007).

3.15
Medicinal plant
plants (wild or cultivated) used for medicinal purposes (WHO, 1996)

3.16
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 (WHO, 2000)

3.17
Active ingredients
the herbal material(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) (WHO, 2000).

3.18
Blending
the process of combining materials or different batches to produce a homogeneous intermediate or finished product (WHO, 2007)

3.19
Constituents with known therapeutic activity
substances or groups of substances which are chemically defined and known to contribute to the therapeutic activity of a herbal material or of a preparation (WHO, 2000)

4 Quality assurance in the manufacture of herbal medicines

4.1 Quality assurance is the totality of the arrangements made with the object of ensuring that herbal products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this standard such as product design and development.

4.2 The system of quality assurance appropriate to the manufacture of herbal products should ensure that:

(a) products are designed and developed in a way that takes account of the requirements of current GMP

(b) production and control operations are clearly specified in a written form and GMP requirements are adopted;

(c) managerial responsibilities are clearly specified in job descriptions;

(d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

(e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;

(f) the finished product is correctly processed and checked, according to the defined procedures;

(g) products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of herbal products;

(h) satisfactory arrangements exist to ensure, as far as possible, that the herbal products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;

(i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;

(j) deviations are reported, investigated and recorded;

(k) there is an internal system for approving changes that may have an impact on product quality;

(l) regular evaluations of the quality of herbal products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

4.3 The manufacturer must assume responsibility for the quality of the herbal products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities.

NOTE The quality assurance system adopted shall take into account the operational extent of the firm, the typical risks involved and the country's infrastructure.

5 Good manufacturing for herbal medicines

5.1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP are aimed primarily at diminishing the risks inherent in any herbal production. Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, false labels being put on containers. Under GMP:

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;

(b) qualification and validation/annual product reviews are performed;

(c) all necessary resources are provided, including:

  (i) competent personnel;

  (ii) adequate premises and space;

  (iii) suitable equipment and services;

  (iv) appropriate materials, containers and labels;

  (v) approved procedures and instructions;

  (vi) suitable storage and transport;

  (vii) adequate personnel, laboratories and equipment for in-process controls;

(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;

(e) operators are trained to carry out procedures correctly;

(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;

(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(h) the proper storage and distribution of the products minimizes any risk to their quality;

(i) a system is available to recall any batch of product from sale or supply;

(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

5.2 Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, are covered by CD-ARS 952-2013. The first critical step of their production where the application of GMP starts should be clearly designated. This is of particular importance for those products which consist solely of comminuted or powdered herbal materials.

5.3 Primary processing

5.3.1 Sorting

All medicinal plant materials shall be inspected during the primary-processing stages of production, and any substandard products or foreign matter eliminated mechanically or by hand for example discoloured, mouldy or damaged materials, as well as soil, stones and any other foreign matter.

5.3.2 Cleaning

Cleaning of all medicinal plant materials shall be done appropriately using clean water free from microbial and chemical contaminants.

5.3.3 Drying where applicable

(i) The harvested material shall be unpacked as soon as possible on arrival at the drying facilities. In certain instances the material shall not be allowed to stand for extended period of time in direct sunlight and shall also be protected from excessive humidity.

(ii) Buildings used for drying the harvested material shall be well ventilated and shall not be used for any other activities.

(iii) The building shall be constructed so as to protect the harvested material from birds, insects, and animals.

(iv) Drying racks shall be kept clean and regularly maintained.

(v) The harvested materials shall be placed in thin layers, on wire mesh racks standing off the floor to allow free air circulation, and stirred intermittently to ensure uniform drying and prevent decomposing.

(vi) Drying on the floor is not recommended.

(vii) Dried harvested materials shall be inspected to remove discoloured, mouldy, damaged material, soil, stones and any other foreign matter.

5.3.4 Storage

(i) The dried material shall be packed in clean appropriate containers. Reusable containers shall be well-cleaned before use.

(ii) The containers shall be stored in a clean dry place off the ground, free from pests and inaccessible to animals.

(iii) Packed dried material shall be stored in a dry, well ventilated building, with minimal variation in diurnal temperature and with good air ventilation. Shutter and door openings shall be protected by wire screens to keep out pests and any other animals.

(iv) It is recommended that packed dried materials shall be stored in a building with concrete floors; on pallets; away from the wall; well separated from all other materials.

6 Sanitation and hygiene

6.1 Because of their origin, herbal materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, herbal products may be especially prone to microbiological contamination. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene during manufacture is necessary.

6.2 Water supply to the manufacturing unit should be monitored, and, treated appropriately to ensure consistency of quality.

6.3 Waste from the manufacturing unit should be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste-bins should be available, emptied and cleaned as needed, but at least daily.

6.4 The appropriate requirements of ARS 53 shall be complied with in the processing and manufacturing operations of herbal medicines.

7 Qualification and validation

7.1 Qualification of critical equipment, process validation and change control are particularly important in the production of herbal medicines with unknown therapeutically active constituents. In this case, the reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches.

7.2 A written procedure should specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

7.3 A formal change control system should be established to evaluate the potential effects of any changes on the quality of the herbal medicines, particularly content of the active ingredients. Scientific judgement should be used to determine which additional testing and validation studies are appropriate to justify a change in a validated process.

8 Complaints

8.1 The person responsible for handling complaints and deciding on the measures to be taken to deal with them should have appropriate training and/or experience in the specific features of the quality control of herbal medicines.

8.2 There are basically two types of complaint, product quality complaints and adverse reactions/events.

8.3 The first type of complaint may be caused by problems such as faulty manufacture, product defects or deterioration as well as, particular to herbal medicines, adulteration of the herbal material. These complaints should be recorded in detail and the causes thoroughly investigated (e.g. by comparison with the reference samples kept from the same batch). There should also be written procedures to describe the action to be taken.

8.4 To address the second type of complaint, reports of any adverse reaction/ event should be entered in a separate register in accordance with national and international requirements. An investigation should be conducted to find out whether the adverse reaction/event is due to a quality problem and whether such reactions/events have already been reported in the literature or whether it is a new observation. In either case, complaint records should be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products. (WHO, 2004) deals with specific issues relating to adverse reactions and adverse events following treatment with herbal medicines.

8.5 The licensing authority should be kept informed of any complaints leading to a recall or restriction on supply and the records should be available for inspection.

9 Product recalls

9.1 There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

9.2 The authorized person should be responsible for the execution and coordination of recalls. He/she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

9.3 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.

9.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.

9.5 All 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.

9.6 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.

9.7 The progress of the recall process should be monitored and recorded. 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.

9.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

10 Contract production and analysis

10.1 The contract partner should have adequate premises and equipment for the production of herbal medicines according to GMP. Validated methods should be applied for cleaning the equipment and premises carefully before using them to produce different herbal medicinal, food or cosmetic products. In the case of raw materials used for producing food, it is realistic to require manufacturing departments to be separated from those where the plant raw material will be cut or powdered for use in the preparation of medicines.

10.2 Technical aspects of the contract should be drawn up by competent persons of herbal medicines, including their production and quality control testing.

11 Self-inspection

11.1 Principle

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may, in addition, be performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced All recommendations for corrective action should be implemented within a specified time period. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

11.2 Items for self-inspection

Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) personnel;

(b) premises including personnel facilities;

(c) maintenance of buildings and equipment;

(d) storage of starting materials and finished products;

(e) equipment;

(f) production and in-process controls;

(g) quality control;

(h) documentation;

(i) sanitation and hygiene;

(j) validation and revalidation programmes;

(k) calibration of instruments or measurement systems;

(l) recall procedures;

(m) complaints management;

(n) labels control;

(o) results of previous self-inspections and any corrective steps taken.

11.3 Self-inspection team

Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines.

11.4 Frequency of self-inspection

The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

11.5 Self-inspection report

A report should be made at the completion of a self-inspection. The report should include:

(a) self-inspection results;

(b) evaluation and conclusions;

(c) recommended corrective actions.

11.6 Follow-up action

There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

11.7 Quality audit

It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

11.8 Suppliers' audits and approval

11.8.1 The person responsible for quality control should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

11.8.2 Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

12 Personnel

12.1 The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of herbal medicinal products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

12.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

12.3 All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should define key persons that should be part of the organization chart.

12.4 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. All personnel should be motivated to support the establishment and maintenance of high quality standards.

12.5 Steps should be taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

12.6 The release of herbal medicines should be authorized by a person who has been trained in the specific features of the processing and quality control of herbal materials, herbal preparations and finished herbal products.

12.7 Personnel dealing with the production and quality control of herbal medicines should have adequate training in the specific issues relevant to herbal medicines.

13 Training

13.1 The personnel should have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of herbal medicines).

13.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.

13.3 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

13.4 The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

13.5 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

13.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

14 Personal hygiene and health

14.1 Health status

(i) All personnel known, or suspected, to be suffering from or to be a carrier of a disease or illness likely to be transmitted through medicinal plant material, shall not be allowed to enter any harvest, production or processing area if there is a likelihood of their contaminating medicinal plant materials.

(ii) Medical examination of personnel shall be carried out if clinically or epidemiologically indicated.

14.2 Illness and injuries

(i) All personnel with open wounds, inflammations or skin diseases shall not be engaged in work or required to wear protective clothing and gloves until full recovery.

(ii) Persons suffering from known airborne or food-borne communicable diseases, including dysentery and diarrhoea, shall not be engaged in work in all areas of production and processing, in accordance with local and/or national regulations.

(iii) Health conditions that shall be reported to the management for consideration regarding medical examination and/or possible exclusion from handling of medicinal plant materials include: jaundice, diarrhoea, vomiting, and fever, sore throat with fever, visibly infected lesions (boils, cuts, etc.) and discharges from the ear, nose or eye.

14.3 Personal cleanliness

14.3.1 Personnel entrusted with the handling of herbal materials, herbal preparations and finished herbal products should be required to have a high degree of personal hygiene, to have received adequate training in maintaining appropriate standards of hygiene and wear suitable protective clothing and gloves, including head covering and footwear. The personnel should not work if they have infectious diseases or skin diseases. Written procedures listing the basic hygiene requirements should be made available.

14.3.2 Personnel must be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing. They should wear suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture.

14.4 Personal behaviour

(i) Smoking and eating shall not be permitted in medicinal plant processing areas.

(ii) Personnel who handle medicinal plant materials shall refrain from behaviours that could result in contamination of the materials, for example, spitting, sneezing or coughing over unprotected materials.

(iii) Personal effects such as jewellery, watches or other items shall not be worn or brought into areas where medicinal plant materials are handled.

14.5 Visitors

Visitors to processing and handling areas shall wear appropriate protective clothing and adhere to all of the personal hygiene provisions mentioned above.

15 Premises

15.1 General

15.1.1 As a general principle, premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to GMP and GHP. The premises shall be so constructed as to provide protection for the harvested material against birds, insects, rodents as well as domestic animals.

15.1.2 Because of their potential for degradation and infestation with certain pests as well as their sensitivity to microbiological contamination, production, and particularly storage, of herbal materials and herbal preparations assume special importance.

15.1.3 The layout and design of premises must 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.

15.1.4 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

15.1.5 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

15.1.6 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

15.1.7 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

15.1.8 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

15.1.9 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

15.1.10 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

15.1.11 Premises should be designed to ensure the logical flow of materials and personnel.

15.2 Ancillary areas

15.2.1 Rest and refreshment rooms should be separate from manufacturing and control areas.

15.2.2 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

15.2.3 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.

15.2.4 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

15.3 Storage areas

15.3.1 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.

15.3.2 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

15.3.3 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

15.3.4 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

15.3.5 Storage areas should be well organized and tidy. Special attention should be paid to cleanliness and good maintenance. Any accidental spillage should be cleaned up immediately using methods that minimize the risk of cross-contamination of other materials, and should be reported.

15.3.6 The set-up of storage areas depends on the type of materials stored. The areas should be well labelled and materials stored in such a way as to avoid any risk of cross-contamination. An area should be identified for the quarantine of all incoming herbal materials.

15.3.7 Storage areas should be laid out to permit effective and orderly segregation of the various categories of materials stored, and to allow rotation of stock. Different herbal materials should be stored in separate areas.

15.3.8 To protect the stored material, and reduce the risk of pest attacks, the duration of storage of any herbal material in unpacked form should be kept to a minimum.

15.3.9 Incoming fresh herbal materials should be processed, unless specified otherwise, as soon as possible. If appropriate, they should be stored between 2 °C and 8 °C, whereas frozen materials should be stored below –18 °C.

15.3.10 Where materials are stored in bulk, to reduce the risk of mould formation or fermentation it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas should also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms brought in with the plant material and to prevent cross-contamination.

15.3.11 Herbal materials, even when stored in fibre drums, bags or boxes, should be stored off the floor and suitably spaced to permit cleaning and inspection.

15.3.12 The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; appropriate steps should be taken to ensure that these conditions are provided, maintained, monitored and recorded.

15.3.13 Herbal materials, including raw herbal materials, should be kept in a dry area protected from moisture and processed following the principle of “first in, first out” (FIFO).

15.4 Weighing areas

The weighing of starting materials and the estimation of yield by weighing should 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.

15.5 Production areas

15.5.1 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities should be available for the production of particular herbal products based on their sensitivity and level of activity. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. Moreover, the special nature of the production of herbal medicines requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism should be employed to prevent accumulation of fumes and vapours.

15.5.2 The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

15.5.3 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.

15.5.4 To facilitate cleaning and to avoid cross-contamination, adequate precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g. by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

15.5.5 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different herbal 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.

15.5.6 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

15.5.7 Pipework, light fittings, ventilation points and other services should 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.

15.5.8 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 should be shallow to facilitate cleaning and disinfection.

15.5.9 Production areas should 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. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

15.5.10 Premises for the packaging of herbal medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

15.5.11 Production areas should be well lit, particularly where visual on-line controls are carried out.

16 Equipment

16.1 Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must 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.

16.2 Processing of herbal materials may generate dust or material which is susceptible to pest-infestation or microbiological contamination and cross-contamination. Effective cleaning of the equipment is therefore particularly important.

16.3 Production equipment should be thoroughly cleaned on a scheduled basis. Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination. 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.

16.4 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

16.5 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 odours, be easily discoloured and are easily contaminated.

16.6 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

16.7 Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different herbal products to prevent cross-contamination.

17 Materials

17.1 General

17.1.1 All incoming herbal materials should be quarantined and stored under appropriate conditions that take into account the degradability of herbal materials and herbal preparations.

17.1.2 Only permitted substances should be used for fumigation, cleaning, lubrication of equipment and pest control and allowable limits for their residues together with specifications for the apparatus used should be set according to the national regulations. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

17.2 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.

17.3 Waste materials

17.3.1 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

17.3.2 Waste material should 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.

18 Documentation

18.1 General

18.1.1 Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to make decisions, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

18.1.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

18.1.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

18.1.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

18.1.5 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.

18.1.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

18.1.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

18.1.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of products are traceable. Records should be retained based on country requirements after the expiry date of the finished product.

18.1.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

18.2 Labels

18.2.1 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).

18.2.2 All finished medicinal products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the medicinal product;

(b) a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);

(c) the batch number assigned by the manufacturer;

(d) the expiry date in an un-coded form;

(e) any special storage conditions or handling precautions that may be necessary;

(f) directions for use, and warnings and precautions that may be necessary;

(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

18.2.3 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.

18.3 Standard operating procedures (SOPs) and records

18.3.1 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

(a) equipment assembly and validation;

(b) analytical apparatus and calibration;

(c) maintenance, cleaning and sanitization;

(d) personnel matters including qualification, training, clothing and hygiene;

(e) environmental monitoring;

(f) pest control;

(g) complaints;

(h) recalls;

(i) returns.

18.3.2 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

18.3.3 The records of the receipts should include:

(a) the name of the material on the delivery note and the containers;

(b) the “in-house” name and/or code of material if different from (a);

(c) the date of receipt;

(d) the supplier’s name and, if possible, manufacturer’s name;

(e) the manufacturer’s batch or reference number;

(f) the total quantity, and number of containers received;

(g) the batch number assigned after receipt;

(h) any relevant comment (e.g. state of the containers).

18.3.4 There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

18.3.5 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.

18.3.6 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

18.3.7 The sampling instructions should include:

(a) the method of sampling and the sampling plan;

(b) the equipment to be used;

(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;

(d) the amount(s) of sample(s) to be taken;

(e) instructions for any required subdivision of the sample;

(f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;

(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

18.3.8 There should be a standard operating procedure describing the details of the 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.

18.3.9 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

18.3.10 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

18.3.11 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.

18.3.12 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.

18.3.13 Analysis records should include at least the following data:

(a) the name of the material or product and, where applicable, dosage form;

(b) the batch number and, where appropriate, the manufacturer and/ or supplier;

(c) references to the relevant specifications and testing procedures;

(d) test results, including observations and calculations, and reference to any specifications (limits);

(e) date(s) and reference number(s) of testing;

(f) the initials of the persons who performed the testing;

(g) the date and initials of the persons who verified the testing and the calculations, where appropriate;

(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

18.3.14 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.

18.3.15 Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.

18.3.16 Records should 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.

18.3.17 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

18.3.18 There should 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. Such written procedures should be followed.

18.4 Specifications

18.4.1 The specifications for herbal starting materials, for herbal preparations and finished herbal products are primarily intended to define the quality rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring safety and efficacy. Consistent quality for herbal medicines (finished herbal products) can only be assured if the starting herbal materials are defined in a rigorous and detailed manner. In some cases more detailed information may be needed on aspects of collection or agricultural production. For instance, the selection of seeds, conditions of cultivation and harvesting are important aspects in producing a reproducible quality of herbal medicines (see CD-ARS 952:2013). Their characterization (which also includes a detailed evaluation of the botanical and phytochemical aspects of the medicinal plant, manufacture of the herbal preparation and the finished herbal product) is therefore essential to allow the establishment of specifications which are both comprehensive and relevant.

18.4.2 Herbal preparations

For this reason, the specifications for herbal preparations should as far as possible include, as a minimum, the following information:

(i) The family and botanical name of the plant used according to the binomial system (genus, species, variety and the authority, i.e. the reference to the originator of the classification, e.g. Linnaeus). It may also be appropriate to add the vernacular name and the therapeutic use in the country or region of origin of the plant.

(ii) Details of the source of the plant, such as country and/or region (also state and province, if applicable) of origin, whether it was cultivated or collected from the wild and, where applicable, method of cultivation, dates and conditions of harvesting (e.g. whether there was extreme weather), collection procedures, collection area, and brand, quantity and date of pesticide application, as required by CD-ARS 952:2013.

(iii) Whether the whole plant or only a part is used. In the latter case, which part of the plant is used and its state, e.g. whole or reduced. For dried plant material, the drying system should be specified, if applicable.

(iv) A description of the plant material based on visual (macroscopic) and/or microscopic examination.

(v) Suitable identity tests including, where appropriate, identification tests (such as TLC or other chromatographic fingerprint) for known active ingredients or markers. A reference sample should be available for identification purposes.

(vi) Details of the assay, where appropriate, of active constituents or markers.

(vii) Limit tests such as dry residue of liquids, ash value (total ash, and ash insoluble in hydrochloric acid), water-soluble extractives, moisture/water content and loss on drying (taking into account the presence of essential oils if any).

(viii) Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination in herbal materials or herbal preparations used in the manufacture of herbal medicines.

(ix) Tests for toxic metals and for likely contaminants, foreign materials and adulterants.

(x) Tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest-infestations, radioactivity and their acceptable limits.

(xi) Other appropriate tests (e.g. particle size, swelling index and residual solvents in herbal preparations and biological fingerprints such as induced fluorescent markers).

18.4.4 Specifications for starting materials (and also of primary or printed packaging materials) should include, if applicable, reference to a pharmacopoeial monograph.

18.4.5 If the herbal material for processing does not comply with its quality specifications, the rules that apply for its rejection, and to storage and disposal of the rejected herbal material should be included.

18.4.6 Starting materials derived from or comprising genetically modified organisms should comply with existing national or international regulations and the label should include this information. Chemical protection of herbal materials should be in accordance with national and/or international regulations (see CD-ARS 952:2013).

18.4.7 Qualitative and quantitative information on the active ingredients or constituents with known therapeutic activity in herbal materials and herbal preparations should be given as described in 20.5.

18.5 Finished herbal products

18.5.1 Finished herbal products shall undergo the following examinations:

(i) Tests for microbiological contamination and tests for other toxicants.

(ii) Uniformity of weight (e.g. for tablets, single-dose powders, suppositories, capsules and herbal tea in sachets), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (tablets or capsules), if applicable.

(iii) Physical appearance such as colour, odour, form, shape, size and texture.

(iv) Loss on drying, or water content.

(v) Identity tests, qualitative determination of relevant substances of the plants (e.g. fingerprint chromatograms).

(vi) Quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available.

(vii) Limit tests for residual solvents.

18.5.2 The control tests and specifications for the finished herbal product should be such as to allow the qualitative and quantitative determination of the main active constituents. If the therapeutic activity of constituents is known, these constituents should be indicated in the documentation. If such substances are not known (e.g. because they are part of a complex mixture), the constituents useful for assessing the quality should be identified as markers. In both cases, the assay (i.e. quantitative determination) specifications should be defined. When the therapeutic activity of the constituents cannot be determined quantitatively, specifications should be based on the determination of markers.

18.5.3 If either the final product or the herbal preparation contains several herbal materials and a quantitative determination of each active ingredient is not feasible, the mixture of several active ingredients may be determined. The need for such a procedure should be justified.

18.5.4 The concept of different acceptance criteria for release versus shelf-life specifications applies to finished herbal medicines only and not to herbal materials and herbal preparations. Adequate retest periods should be established for the latter. Examples where this may be applicable include assay and impurity (degradation product) levels.

18.6 Herbal preparations

The specifications of herbal preparations consist, depending on the preparation in question, of the relevant items of the specifications for herbal materials or for finished herbal products as outlined above.

18.7 Processing instructions

18.7.1 The processing instructions should describe the different operations to be performed on the plant material, such as drying, crushing, milling and sifting. They should also include the time and, if applicable, temperatures required in the drying process, and the methods to be used to control fragment or particle size. Instructions on removing foreign matters and other unwanted materials should also be given.

18.7.2 The drying conditions chosen should be appropriate to the type of plant material processed. These depend on both the character of the active ingredients (e.g. essential oils) and the type of plant part collected (e.g. root, leaf or flower). Drying by direct exposure to sunlight, if not specifically contraindicated, is possible, but drying on the ground should be avoided. If the plant should be processed fresh, without drying, the reasons and criteria determining the use of fresh material should be stated.

18.7.3 For the production of processed extracts, the instructions should specify details of any vehicle or solvent that may be used, the durations and temperatures needed for extraction, and any concentration stages and methods that may be required.

18.7.4 The permissible environmental conditions e.g. temperature, humidity and standard of cleanliness, should be stated.

18.7.5 Any treatment, such as fumigation, used to reduce fungal or microbiological contamination or other infestation, together with methods of determining the extent of such contamination and potential residues, should be documented. Instructions on the conduct of such procedures should be available and should include details of the process, tests and allowable limits for residues together with specifications for apparatus used.

18.7.6 Steps in the processes of blending and adjustment to reach defined contents of pharmacologically active constituents should be clearly documented.

18.7.7 The rules that apply to the disposal of spent herbal material after processing should also be elaborated.

19 Good practices in production

19.1 General

To ensure the quality, the safety and efficacy of herbal medicines, it is essential that the steps in their production are clearly defined.

19.2 Selection of the first production step covered by these guidelines

19.2.1 For medicinal plants — which are either cultivated or collected from the wild, and which may be used in crude form or subjected to simple processing techniques (such as cutting or comminuting) — the first critical step of their production, i.e. where the application of these guidelines starts, should be clearly designated. The rationale for this designation should be stated and documented. Guidance is provided below. However, for processes such as extraction, fermentation and purification, this rationale should be established on a case-by-case basis.

(i) Collection/cultivation and/or harvesting of medicinal plants should follow other relevant guidance such as CD-ARS 952:2013.

(ii) Generally, postharvest processing including primary cutting is (or should be) covered by GACP. If further comminuting is carried out in the manufacturing processing, it should be covered by GMP, or by these supplementary guidelines. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of herbal materials, application of these supplementary guidelines may be extended to encompass these steps.

(iii) When the active ingredient consists exclusively of comminuted or powdered herbs, application of these guidelines starts at the physical processing following primary cutting and comminuting, and includes packaging.

(iv) When herbal extracts are used, the principles of these guidelines should apply to any production step following postharvest processing.

(v) In the case of finished herbal products manufactured by fermentation, application of GMP should cover any production step following primary cutting and comminuting. Particular attention should be given to the introduction of cells from a cell bank into the fermentation process.

19.3 General considerations

19.3.1 Materials should be handled in a fashion that is not detrimental to the product. On arrival at the processing facility, the herbal material should be promptly unloaded and unpacked. During this operation, the herbal material should not come into direct contact with the soil. Moreover, it should not be exposed directly to the sun (except in cases where this is a specific requirement, e.g. sun-drying) and it should be protected from rain and microbiological contamination.

19.3.2 Attention should be paid to “classification” of clean area requirements taking into account the possible high degree of initial microbial contamination of herbal materials. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to processing of herbal materials. Specific and detailed requirements should be developed to cover microbial contamination of equipment, air, surfaces and personnel, and also for rest rooms, utilities, ancillary and supporting systems (e.g. water and compressed air).

19.3.3 Care should be taken to choose cleaning methods appropriate to the characteristics of the herbal materials being processed. Washing dried herbal materials with water is generally

inappropriate. When it is necessary to clean them, an air duster or air shower should be employed. In cases when immersion of herbal materials in water or other appropriate agents (such as disinfectants) for cleaning is unavoidable (e.g. to eliminate suspected coliform bacteria), it should be kept to a minimum.

19.3.4 The presence of plant materials from different species and varieties, or different plant parts should be controlled during the entire production process to avoid contamination, unless it is assured that these materials are equivalent.

19.3.5 If time limits are specified in the master production instructions, these limits should not be exceeded, to ensure the quality of intermediates and finished products. The less is known about the constituents responsible for the therapeutic activity, the more strictly this rule should be obeyed. Such time limits, however, may be inappropriate when processing to achieve a target value (e.g. drying to a predetermined specification) because completion of processing steps is determined by in-process sampling and testing.

19.4 Mixing of batches and blending

19.4.1 Herbal medicines with constituents of known therapeutic activity are often standardized (i.e. adjusted to a defined content of such constituents). The methods used to achieve such standardization should be documented.

If another substance is added for these purposes, it is necessary to specify, as a range, the quantity that may be added. Blending different batches of a specific herbal material (e.g. before extraction) or by mixing different lots of similar herbal preparations may also be acceptable. Records should be maintained to ensure traceability. The blending process should be adequately controlled and documented and the blended batch should be tested for conformity with established specifications where appropriate.

19.4.2 Batches should be mixed only if it can be guaranteed that the mixture will be homogeneous. Such processes should be well documented.

19.4.3 Out-of-specification batches of herbal medicines should not be blended with other batches for the purpose of meeting specifications, except for standardization of the content of constituents with known pharmaceutical therapeutic effect. Every batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

19.4.4 Where particular physical attributes of the material are critical, blending operations should be validated to show uniformity of the combined batch. Validation should include testing of critical attributes (e.g. particle size distribution, bulk density and tap density) that may be affected by the blending process.

19.4.5 The expiry date of the blended batch should be chosen according to the date of manufacture of the oldest batch in the blend.

20 Good practices in quality control

20.1 General

20.1.1 The personnel of quality control units should have the necessary expertise in herbal medicines to enable them to carry out identification tests and recognize adulteration, the presence of fungal growth or infestations and lack of uniformity in a consignment of herbal materials.

20.1.2 The quality control of the herbal material, herbal preparations and finished herbal products should establish their quality but does not imply the control of every single constituent

20.2 Sampling

20.2.1 Because herbal materials are an aggregate of individual plants and/ or different parts of the same plant and thus have an element of heterogeneity, sampling should be carried out with special care by personnel with the necessary expertise.

20.2.2 Further advice on sampling and visual inspection is given in *Quality control methods fro herbal materials* (WHO: 2011)

20.3 Testing

20.3.1 The identity and quality of herbal material, herbal preparations and of finished herbal products should be tested as described in (WHO: 2011). The minimum requirement for the technical equipment is for instruments to perform the tests described in (WHO 2011). Moreover, each country should develop this basic requirement for technical equipment further, according to the country's needs.

20.3.2 Herbal material, herbal preparations (including extracts) and finished herbal products can be categorized as follows:

(a) the active constituents are identified, and may be quantified as such;

(b) the main group of components which contribute to the activity (i.e. the constituents with known therapeutic activity) are known and can be quantified as a total (e.g. essential oils) or calculated using a representative substance belonging to the group (e.g. flavonoids);

(c) the former are not identified and/or not quantifiable, but marker substances are;

(d) others, where quantification (i.e. specification for a certain quantity of a constituent) is not applicable or feasible.

20.3.3 Identification methods may be based on:

(i) physical and, if applicable, macroscopic (organoleptic) and microscopic tests;

(ii) chromatographic procedures (TLC, HPLC, HPTLC or gas–liquid chromatography (GLC)), spectrometric techniques (ultraviolet-visible (UV-VIS), IR, nuclear magnetic resonance (NMR), MS); and/or

(iii) chemical reactions.

20.3.4 The identification test methods should be specific for the herbal material, herbal preparation or finished herbal product and ideally should be capable of discriminating between the required herbal material and potential substitutes or adulterants that are likely to occur. The identification methods used for groups (a) and (b) should be capable of detecting the said active ingredients and at least the main ingredients should be stated on the label. For group (c), the analytical procedure should be based on characteristic constituents, if any.

20.3.5 Reference samples of herbal materials should be made available for use in comparative tests, e.g. visual and microscopic examination and chromatography.

20.3.6 Quantitative determination of known active components for members of groups (a) and (b) and of markers for members of group (c) is necessary.

20.3.7 The development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products should be in line with 18.4. Tests and quality requirements that are characteristic of the given analyte should be selected.

20.3.8 Particularly for herbal materials in group d and for finished herbal products containing such materials, characteristic chromatograms (and/or fingerprint chromatograms) may be applicable. Using these methods may ensure that the main constituents can be easily followed throughout the production process. Caution is necessary, however, for every delivery of herbal materials and every

batch of herbal preparations (including extracts) will have slightly different chromatograms/fingerprints resulting from differences in chemical compositions caused by intrinsic or extrinsic factors.

20.4 Stability studies

20.4.1 If the expiry date for a herbal material or herbal preparation is given, some stability data to support the proposed shelf-life under the specified storage conditions should be available. Stability data are always required to support the shelf-life proposed for the finished herbal products.

20.4.2 Finished herbal products may contain several herbal materials or herbal preparations, and it is often not feasible to determine the stability of each active ingredient. Moreover, because the herbal material, in its entirety, is regarded as the active ingredient, a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Chromatography allows tracing of changes which may occur during storage of a complex mixture of biologically active substances contained in herbal materials. It should be shown, as far as possible, e.g. by comparisons of appropriate characteristic/fingerprint chromatograms, that the identified active ingredient (if any) and other substances present in the herbal material or finished herbal product are likewise stable and that their content as a proportion of the whole remains within the defined limits.

20.4.3 The fingerprint methods used for the stability studies should be as similar as possible to those used for quality control purposes.

20.4.4 For identified active ingredients, constituents with known therapeutic activity and markers, widely used general methods of assay, and physical and sensory or other appropriate tests may be applied.

20.4.5 To determine the shelf-life of finished herbal products, strong emphasis should also be placed on other tests in 18.4, such as moisture content, microbial contamination and general dosage form control tests.

20.4.6 The stability of preservatives and stabilizers should be monitored. When these are not used, alternative tests should be done to ensure that the product is self-preserving over its shelf-life.

20.4.7 Samples used for stability studies should be stored in the containers intended for marketing.

20.4.8 Normally the first three commercial production batches should be included in the stability-monitoring programme to confirm the expiry date. However, where data from previous studies, including pilot batches, show that the product is expected to remain stable for at least two years, fewer than three batches can be used. The testing frequency depends on the characteristics of the herbal medicinal products and should be determined on a case-by-case basis.

20.4.9 The protocol for ongoing stability studies should be documented. This would normally involve one batch per year being included in a stability-monitoring programme.

20.5 Packaging materials and labelling

20.5.1 All processed herbal medicines shall be packed in food grade containers that protect the product from any form of contamination or deterioration and labelled. All packaging materials, such as bottles and other materials, should be stored properly. Controls on the issue and use of these packaging materials should be adequate to ensure that incorrect labels and cartons are not used.

20.5.2 All containers and closures should be thoroughly cleaned and dried before being used to pack the products.

20.5.3 There should be adequate information on the label (or the package insert) to inform the users of the composition of the product (in addition to the brand name, if any), indications or actions, directions for use, cautions and adverse reactions if any, and the expiry date.

20.5.4 Finished herbal products may contain several herbal materials and/ or herbal preparations. Unless otherwise fully justified, the full quantitative composition of the herbal ingredients should be

stated on the product label. If this is not possible, at least the main ingredients should be stated on the label while the full qualitative composition could appear on the package insert.

20.5.5 The qualitative and quantitative particulars of the active ingredients in herbal materials and herbal preparations should be expressed in the following ways:

(a) For herbal materials and herbal preparations consisting of comminuted or powdered herbal materials:

(i) the quantity of the herbal material must be stated or, if constituents with known therapeutic activity are unidentified, the quantity of the herbal material/herbal preparation should be stated; or

(ii) the quantity of the herbal material/herbal preparation should be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see examples).

Examples:

(a)

Name of the active ingredient or active plant materials	*Quantity of constituent*
Valerianae radix	900 mg

(b)

Name of the active ingredient or active herbal materials	*Quantity of constituent*
	415–500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

(b) For herbal preparations produced by steps, which exceed comminution, the nature and concentration of the solvent and the physical state of the extract should be given. Furthermore, the following should be indicated:

(i) the equivalent quantity or the ratio of a herbal material to herbal preparation must be stated if therapeutic activity of the constituents is unknown (this does not apply to fatty or essential oils); or

(ii) if the therapeutic activity of the constituents is known, the quantity of the herbal preparation may be given as a range, corresponding to a defined quantity of the constituents with known therapeutic activity (see examples).

Examples:
(a)

Name of the active substance or active herbal materials	*Quantity of constituent*
Valerianae radix	25 mg dry ethanolic (96% v/v) extract (8:1) or 125 mg ethanolic (96% v/v) extract, equivalent to 1000 mg of *Valerianae radix*
other ingredient	20–50 mg
Dextrin	

(b)

Name of the active substance or active herbal materials	*Quantity of constituent*
Sennae folium	100–130 mg dry ethanolic (96% v/v)

	extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B
other ingredient	
Dextrin	20–50 mg

20.5.6 The composition of any solvent or solvent mixture used and the physical state of the extract should be identified.

20.5.7 If any other substance is added during the manufacture of the herbal preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) should be described as such or as "other ingredients" and the genuine extract as the "active ingredient". However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content or for any other purpose, the final mixture should be regarded as the genuine extract and listed as the "active ingredient" in the unit formula.

20.5.8 Labelling

In addition to the requirements of ARS 56, the following information shall appear in legible and indelible marking on a label on the package and/or a package insert.

(i) Name of the product.

(ii) Ingredients in descending order of proportion.

(iii) Declaration of active ingredients or name of the plant.

(iv) Name and physical address of the manufacturer.

(v) Net content in metric units.

(vi) Warning statement indicating that herbal medicines shall be kept out of reach of children.
Contra-indications
Side effects
Precautions
Instructions for use.

(vii) Dosage per age of an individual.

(viii) Instructions for storage.

(ix) Instructions for disposal.

(x) Manufacturing date.

(xi) Batch number

(xii) Expiry date.

(xiii) Containers used shall be appropriate with child proof seals.

20.5.9 Storage

Medicinal plant materials shall be protected from contamination and decomposition as well as from insects, rodents, birds and other pests, and from livestock and other domestic animals

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