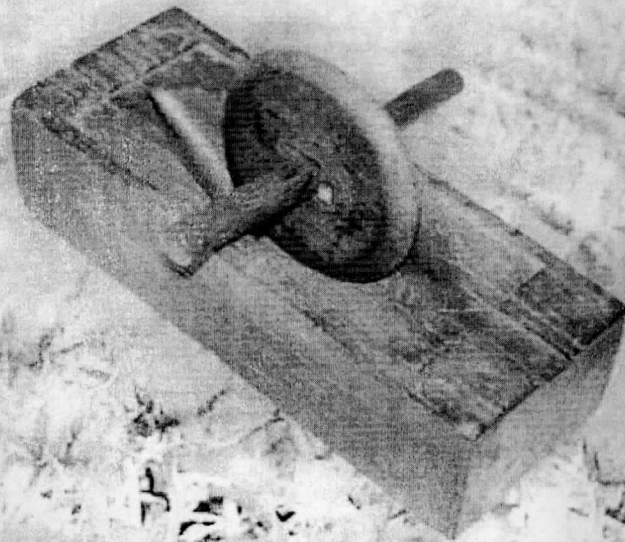


**WHO guidelines
on good manufacturing
practices (GMP)
for herbal medicines**



**World Health
Organization**

**WHO guidelines on
good manufacturing practices (GMP) for
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Organization**

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Preface

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.

The latest World Health Assembly resolution on traditional medicine (WHA56.31) requested WHO to provide technical support to develop methodology to monitor or ensure the quality, efficacy and safety of products. The quality of herbal medicines can directly affect their safety and efficacy. Member States face complicated technical issues in the quality control of herbal medicines. In order to promote and improve the quality of herbal medicines and also to reduce the proportion of adverse events attributable to the poor quality of herbal medicines, WHO has committed to the development of a series of technical guidelines related to quality assurance and control of herbal medicines, as well as to updating existing guidelines.

The manufacturing process is one of the key steps where quality control is required to ensure quality of medicinal products, including herbal medicines. Good manufacturing practices (GMP) is one of the most important tools for this measure.

The core requirements for GMP for herbal medicines are common to GMP for pharmaceutical products. In 1996, WHO issued "Good manufacturing practices: supplementary guidelines for the manufacture of herbal medicinal products".¹ However, at that time, not many Member States were considering GMP requirements for herbal medicines, and only key technical issues were presented. The increasing use of herbal medicines has led to further research on them and to the development of techniques for their quality control. In addition, more and more Member States have started to establish their own national GMP specific for herbal medicines. Therefore it became desirable for WHO to update the Good Manufacturing Practices (GMP) supplementary guidelines for manufacture of herbal medicines. These updated guidelines were finalized in 2005 and adopted by a WHO Expert Committee in 2006, leading to publication as annex 3 of WHO Technical Report Series, No. 937 (2006). In addition, WHO has also updated its core guidelines on GMP, which were published as annex 4 of WHO Technical Report Series, No. 908 (2003). As a whole, GMP control for herbal medicines needs to meet the technical requirements of both sets of guidelines. In order to

¹ WHO Technical Report Series, No. 863, 1996.

consolidate the information and to make such technical guidance user-friendly, it was proposed to compile a WHO monograph on GMP for herbal medicines, which combines these two sets of technical guidelines. This will also serve as a key resource for technical training programmes in capacity building in herbal medicines.

The present consolidated guidelines include, "Core WHO GMP" and "WHO updated GMP: supplementary guidelines for manufacture of herbal medicines", which are reproduced from the respective annexes of the WHO Technical Reports. This volume also contains the contents page of the "Quality Assurance Compendium Vol. 2, 2nd update (2007)", a publication which includes all of the GMP texts published to date, in order to enable full cross-referencing to the WHO GMP, as the GMP guidelines on validation and water, in particular, might also be necessary to those manufacturing herbal medicines.

Note

There is no doubt that GMP is a key step in ensuring the safety and efficacy of herbal medicines. However, meeting GMP requirements requires investment from manufacturers and this may be especially difficult for small manufacturers in developing countries. Investing in GMP may increase production costs, leading to an increase in the price of the final product. This will impact on the affordability of the medicines. Therefore, relevant national health authorities need to take this impact into consideration and take the appropriate measures to encourage and ensure that manufacturers are willing and able to improve their GMP. According to the experiences of some countries, giving a transition period to manufacturers for them to improve the GMP is one good example. Therefore, these guidelines are only a reference and the relevant national health authorities should, based on these guidelines, further develop their own GMP requirements according to their circumstances.

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Section I

WHO good manufacturing practices (GMP): updated supplementary guidelines for the manufacture of herbal medicines¹

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Introduction

Following the publication of the last revised WHO guidelines on *Good manufacturing practices for pharmaceutical products: main principles (1)*, supporting and supplementary guidelines were developed to address specific issues connected with the manufacture of certain types of pharmaceutical product. As part of this series, the WHO *Supplementary guidelines for the manufacture of herbal*

¹ Reproduced in its entirety from WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 3.

medicinal products (2) were issued in 1996. The guidelines were also reproduced in the second volume of the WHO compendium on *Quality assurance of pharmaceuticals* (3). Related WHO documents such as *Guidelines for the assessment of herbal medicines* (4), *General Guidelines for methodologies on research and evaluation of traditional medicine* (5), *Quality control methods for medicinal plant materials* (6), *Guidelines on good agricultural and collection practices for medicinal plants* (7) were also issued.

WHO's *Good manufacturing practices: main principles for pharmaceutical products* were updated in 2003 (1, 8). Around the turn of the millennium, various product-specific good manufacturing practice (GMP) guidelines covering herbal medicines were developed by several WHO Member States, and by the European Union. They covered several issues relevant to the production and quality control of herbal medicines in more detail. For this reason, within the framework of the *WHO Traditional Medicine Strategy: 2000-2005*, revision of the present supplementary guidelines was considered desirable; this was also endorsed by the WHO Expert Committee on Pharmaceutical Specifications at its meetings in 2002, 2003 and 2004.

These guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products* (1), which are reproduced in section II of this book, and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements set out in section II. They relate specifically to the production and control of herbal medicines, insofar as they mainly focus on identifying the critical steps needed to ensure good quality. Therefore the structure of these supplementary guidelines follows that of WHO's GMP main principles.

The supplementary guidelines are intended to provide WHO Member States with general and minimum technical requirements for quality assurance and control in the manufacture of herbal medicines. Each Member State should develop its own national GMP for manufacturing herbal medicines that are appropriate to the country's actual situation.

These supplementary guidelines deal exclusively with herbal medicines. Combination of herbal materials with animal materials, mineral materials, chemicals and other substances is not covered in these guidelines.

General

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 has a direct influence on the quality of herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.

Glossary

Established terms such as batch, bulk, intermediate product, qualification, starting material and validation are used as defined in the Glossary to the *WHO good manufacturing practices for pharmaceutical products: main principles* (see Section II).

The definitions given below apply to the terms as used in these guidelines. These terms and their definitions have been selected and adopted from other WHO documents and guidelines that are widely used by the WHO Member States (1, 2, 5, 7, 8). However, they may have different meanings in other contexts.

It should be noted that, as a consequence of the various types of "herbal medicines", the same type of material may be classified, depending on the case, in different ways (e.g. powdered plant material may be both *herbal material* and *herbal preparation* or, in a packed form, *herbal medicinal product*).

active ingredients (5)

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).

blending

Blending is the process of combining materials or different batches to produce a homogeneous intermediate or finished product.

constituents with known therapeutic activity (5)

Constituents with known therapeutic activity are 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.

herbal medicines (5)

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products.

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.

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials

may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other materials (5).

Herbal preparations are the basis for finished herbal products and may include comminuted or cut herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products consist of herbal preparations made from one or more herbs. 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 (5).

markers

Markers are 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.

medicinal plant (2)

Medicinal plants are plants (wild or cultivated) used for medicinal purposes.

medicinal plant materials - see herbal materials (2)

therapeutic activity (5)

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.

1. Quality assurance in the manufacture of herbal medicines

In addition to the use of modern analytical techniques (especially high performance thin-layer chromatography (HPTLC), gas chromatography (GC), high performance liquid chromatography (HPLC), capillary electrophoresis (CE), mass spectrometry (MS) and atomic absorption (AA) to characterize herbal medicines, quality assurance also requires the control of starting materials, storage and processing. For this reason, an appropriate quality assurance system should be applied in the manufacture of herbal medicines.

Note: The methods of choice may depend on the country's infrastructure.

2. Good manufacturing practice for herbal medicines

2.1 The general principles of GMP are set out in the parent guidelines (see section II). Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, are covered by other guidelines (7). The first critical step of their production where the application of GMP starts should be clearly designated (see subsection 16.1). This is of particular importance for those products which consist solely of comminuted or powdered herbal materials.

3. Sanitation and hygiene

3.1 Because of their origin, herbal materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, herbal products that may be especially prone to microbiological contamination are produced. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene during manufacture is necessary (for guidelines on personal hygiene see section 11, and for those on sanitation see section 12).

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

3.3 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.

4. Qualification and validation

4.1 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.

4.2 The 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.

4.3 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.

5. Complaints

5.1 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.

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

5.3 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.

5.4 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. The *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems* deal with specific issues relating to adverse reactions and adverse events following treatment with herbal medicines (9).

5.5 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.

6. Product recalls

6.1 The product recall procedure depends very much on the national regulations. There should be a standard operating procedure (SOP) for storage of recalled herbal medicines in a secure segregated area, complying with the requirements specified under subsection 12.1 (Storage areas), while their fate is decided.

7. Contract production and analysis

7.1 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.

7.2 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable on the specific characteristics of herbal medicines, including their production and quality control testing.

8. Self-inspection

8.1 At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines.

9. Personnel

9.1 General guidance in relation to personnel involved in the manufacture of medicinal products is given in the parent guide (see section II).

9.2 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.

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

10. Training

10.1 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).

10.2 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

11. Personal hygiene

11.1 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 and to have received adequate training in maintaining appropriate standards of hygiene. The personnel should not work if they have infectious diseases or skin diseases. Written procedures listing the basic hygiene requirements should be made available.

11.2 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.

12. Premises

12.1 As a general principle, premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to *WHO good manufacturing practices for pharmaceutical products: main principles* (see section II).

12.2 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.

Storage areas

12.3 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.

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

12.5 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.

12.6 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.

12.7 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.

12.8 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.

12.9 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.

12.10 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.

12.11 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).

Production areas

12.12 Production areas should comply with the general requirements of *WHO good manufacturing practices for pharmaceutical products: main principles* (see Section II). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. 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.

12.13 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.

13. Equipment

13.1 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.

13.2 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 done with care and avoided if possible, as these methods increase the risk of product contamination.

13.3 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.

14. Materials

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

14.2 Only permitted substances should be used for fumigation, and allowable limits for their residues together with specifications for the apparatus used should be set according to the national regulations.

Reference samples and standards

14.3 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.

15. Documentation

15.1 The general principles for documentation are set out in the *WHO good manufacturing practices for pharmaceutical products: main principles* (see section II).

Specifications

15.2 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 (7). 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.

15.3 For this reason, in addition to the data called for in *WHO good manufacturing practices for pharmaceutical products: main principles* (see section II), the specifications for herbal materials should as far as possible include, as a minimum, the following information:

15.4 *Herbal materials*

- 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.
- 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 the *WHO Guideline on good agricultural and collection practices* (7).

- 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.
- A description of the plant material based on visual (macroscopic) and/or microscopic examination.
- 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.
- Details of the assay, where appropriate, of active constituents or markers.
- 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).
- 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.
- Tests for toxic metals and for likely contaminants, foreign materials and adulterants.
- Tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest-infestations, radioactivity and their acceptable limits.
- Other appropriate tests (e.g. particle size, swelling index and residual solvents in herbal preparations and biological fingerprints such as induced fluorescent markers).

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

15.6 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.

15.7 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 (7).

15.8 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 subsection 17.5 (labelling).

15.9 *Finished herbal products*

- Tests for microbiological contamination and tests for other toxicants.

- 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.
- Physical appearance such as colour, odour, form, shape, size and texture.
- Loss on drying, or water content.
- Identity tests, qualitative determination of relevant substances of the plants (e.g. fingerprint chromatograms).
- Quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available.
- Limit tests for residual solvents.

15.10 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.

15.11 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.

15.12 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.

15.13 *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.

Processing instructions

15.14 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 matter and other unwanted materials should also be given.

15.15 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.

15.16 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.

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

15.18 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.

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

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

16. Good practices in production

16.1 To ensure not only the quality, but also the safety and efficacy of complex products of biological origin such as herbal medicines, it is essential that the steps in their production are clearly defined.

Selection of the first production step covered by these guidelines

16.2 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.

- Collection/cultivation and/or harvesting of medicinal plants should follow other relevant guidance such as the WHO *Guideline on good agriculture and collection practices (GACP) for medicinal plants* (7) or a national guideline.
- 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.

- When the active ingredient, as defined in the Glossary, consists exclusively of comminuted or powdered herbs, application of these guidelines starts at the physical processing following primary cutting and comminuting, and includes packaging.
- When herbal extracts are used, the principles of these guidelines should apply to any production step following postharvest processing.
- 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.

General considerations

16.3 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.

16.4 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).

16.5 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.

16.6 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.

16.7 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.

Mixing of batches and blending

16.8 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.

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

16.10 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.

16.11 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.

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

17. Good practices in quality control

17.1 General

17.1.1 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.

17.1.2 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.

17.2 Sampling

17.2.1 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.

17.2.2 Further advice on sampling and visual inspection is given in the WHO document *Quality control methods for medicinal plant materials* (6).

17.3 Testing

17.3.1 The identity and quality of herbal material, herbal preparations and of finished herbal products should be tested as described in *the Quality control methods for medicinal plant materials* (6). The minimum requirement for the technical equipment is for instruments to perform the tests described in (6). Moreover, each country should develop this basic requirement for technical equipment further, according to its own needs.

17.3.2 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.

17.3.3 Identification methods may be based on:

- physical and, if applicable, macroscopic (organoleptic) and microscopic tests;
- chromatographic procedures (TLC, HPLC, HPTLC or gas-liquid chromatography (GLC)), spectrometric techniques (ultraviolet-visible (UV-VIS), IR, nuclear magnetic resonance (NMR), MS); and/or
- chemical reactions.

17.3.4 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.

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

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

17.3.7 The development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products

should be in line with subsection 15.1 (Specifications). Tests and quality requirements that are characteristic of the given analyte should be selected.

17.3.8 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.

17.4 *Stability studies*

17.4.1 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.

17.4.2 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 characteristics/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.

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

17.4.4 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.

17.4.5 To determine the shelf-life of finished herbal products, strong emphasis should also be placed on other tests in subsection 15.1 (Specifications), such as moisture content, microbial contamination and general dosage form control tests.

17.4.6 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.

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

17.4.8 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.

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

17.5 *Packaging materials and labelling*

17.5.1 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.

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

17.5.3 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.

17.5.4 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.

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

- For herbal materials and herbal preparations consisting of comminuted or powdered herbal materials:
 - a. 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
 - b. 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)

| <i>Name of the active ingredient or active plant materials</i> | <i>Quantity of constituent</i> |
|--|--------------------------------|
| <i>Valerianae radix</i> | 900 mg |

(b)

| <i>Name of the active ingredient or active plant materials</i> | <i>Quantity of constituent</i> |
|--|---|
| <i>Sennae folium</i> | 415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside 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:
 - a. 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
 - b. 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)

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

(b)

| <i>Name of the active substance or active herbal materials</i> | <i>Quantity of constituent</i> |
|--|---|
| <i>Sennae folium</i> | 100-130 mg dry ethanolic (96% v/v) extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B |
| <i>other ingredient</i> | |
| Dextrin | 20-50 mg |

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

17.5.7 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.

References

1. Good Manufacturing Practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4.
2. Good Manufacturing Practices: supplementary guidelines for the manufacture of herbal medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863), Annex 8.
3. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2*. Geneva, World Health Organization, 1999 (Volume 2, Updated edition, 2004).
4. Guidelines for the assessment of herbal medicines. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863), Annex 11. These guidelines were reproduced in *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 1*. Geneva, World Health Organization, 1997.
5. *General guidelines for methodologies on research and evaluation of traditional medicine*. Geneva, World Health Organization, 2000.
6. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
7. *WHO Guideline on good agricultural and collection practices (GACP) for medicinal plants*. Geneva, World Health Organization, 2003.
8. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Updated edition*. Geneva, World Health Organization, 2004.
9. *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems*. Geneva, World Health Organization, 2004.