



WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE

## Final Draft: GOOD MANUFACTURING PRACTICES: UPDATED SUPPLEMENTARY GUIDELINES FOR THE MANUFACTURE OF HERBAL MEDICINES

---

Traditional Medicine  
Department of Technical Cooperation for Essential Drugs and Traditional Medicine  
World Health Organization  
July 2005

---

TITLE: Final draft: Good Manufacturing Practices: updated supplementary guidelines for the manufacture of herbal medicinal products, July 2005

© World Health Organization 2005

All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned staff and member organizations) without the permission of WHO. The draft should not be displayed on any website.

Please send any request for permission to:

Ms Yukiko Maruyama, Scientist, Traditional Medicine (TRM), Department of Technical Cooperation for Essential Drugs and Traditional Medicine (EDM), World Health Organization, 1211 Geneva 27 Switzerland  
FAX: (41-22) 791 4730 E-mail: [trm@who.int](mailto:trm@who.int)

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this draft is complete and correct and shall not be liable for any damages incurred as a result of its use.

**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/04.050/REV.3:****GOOD MANUFACTURING PRACTICES: UPDATED SUPPLEMENTARY****GUIDELINES FOR THE MANUFACTURE OF HERBAL MEDICINES**

	<b>Deadline</b>
First draft prepared	June 2002
First global review	2002-2003
Discussion at WHO Working group meeting on quality control of herbal medicines, Vancouver, Canada	February 2004
Revised draft	July 2004
Second global review	August-October 2005
Second revised draft	May 2005
Discussion at WHO consultation on quality control of herbal medicines, Abu Dhabi, UAE	June 2005
Final draft	July 2005
Mailing for information	September 2005
Presentation to Fortieth WHO Expert Committee on Specifications for Pharmaceutical Preparations	24-28 October 2005

## Table of contents

Introduction.....	3
General.....	3
Glossary.....	4
1. Quality assurance in the manufacture of herbal medicinal products.....	5
2. Good manufacturing practice for herbal medicinal products.....	6
3. Sanitation and hygiene.....	6
4. Qualification and validation .....	6
5. Complaints .....	7
6. Product recalls.....	7
7. Contract production and analysis.....	7
8. Self-inspection.....	8
9. Personnel .....	8
10. Training .....	8
11. Personal hygiene.....	8
12. Premises.....	9
12.1 Storage areas.....	9
12.2 Production areas.....	10
13. Equipment.....	10
14. Materials.....	10
14.1 Reference samples and standards .....	10
15. Documentation.....	11
15.1 Specifications.....	11
15.2 Processing instructions.....	13
16. Good practices in production.....	14
16.1 Selection of the first production step covered by this guideline.....	14
16.2 General considerations.....	14
16.3 Mixing of batches and blending.....	15
17. Good Practices in quality control.....	16
17.1 General.....	16
17.2 Sampling.....	16
17.3 Testing.....	16
17.4 Stability studies.....	17
17.5 Packaging materials and labelling.....	18
References.....	20

## Introduction

Following the publication of the last revised WHO guidelines *Good Manufacturing Practices: main principles for pharmaceutical products (1)*, its supporting and supplementary guidelines were developed to address specific issues connected with the manufacture of certain types of pharmaceutical products. In this series, the WHO *Supplementary guidelines for the manufacture of herbal medicinal products (2)* was issued in 1996. It was reproduced also 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 practice: main principles for pharmaceutical products (1) has been updated in 2003 (8, 9). Around the turn of the millenium, various product specific Good Manufacturing Practice (GMP) guidelines covering herbal medicines, were developed by several WHO Member States, and a regional body such as 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 decided, which was also endorsed by the WHO Expert Committee on Pharmaceutical Specifications in its sessions held in 2002, 2003, and 2004.

These guidelines are intended complement those provided in *Good manufacturing practices for pharmaceutical products (8)* 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 (8). They relate specifically to the production and control of herbal MEDICINES, insofar as they mainly focus on identifying those critical steps that are needed to ensure good quality. Therefore the structure of these supplementary guidelines follows the one employed in the WHO's GMP main principles (8). These guidelines should be considered in conjunction with the above-mentioned main principles (8).

The supplementary guidelines are to provide general and minimum technical requirements for quality assurance and control in manufacturing herbal medicines as a reference to WHO Member States. Each Member State should develop their own national GMP for manufacturing herbal medicines according to the country's actual situation.

These supplementary guidelines deal with herbal medicines exclusively. 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 materials, 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 compo-

sition and properties. Furthermore, in the manufacture and quality control of herbal medicines, procedures and techniques are often used which are 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 good manufacturing practices 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, validation, etc. are used as defined in WHO document (8).

The definitions given below apply to the terms 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 (2, 5, 7, 8, 9). 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 homogenous intermediate or finished product.

### *constituents with known therapeutic activity (5)*

Constituents with known therapeutic activity are substances or group of substances which are chemically defined and known to contribute to the therapeutic activity of an 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 and 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. In the first case, 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 found or are uncertain, 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), atomic absorption (AA) etc., (Note: The methods of choice may be depended on the country's infrastructure) 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.

## 2. Good manufacturing practice for herbal medicines

The general principles of GMP are set out in the parent guidelines (8). Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, are covered by another guidelines (7). The first critical step of their production where the application of good manufacturing practice starts should be clearly designated (see subtitle 16.1). This is of particular importance for those products which consist solely of comminuted or powdered herbal materials.

## 3. Sanitation and hygiene

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

Water supply to manufacturing unit should be monitored, and, if necessary treated appropriately to ensure consistency of quality. Disposal of waste from manufacturing unit should be ensured routinely so as to maintain a high degree 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

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 can mainly ensure the batch-to-batch consistency of quality, efficacy and safety.

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

A formal change control system should be established to evaluate any changes that may affect the quality of the herbal medicines, particularly content of the active ingredients. The potential

impact of the proposed change on the quality should be evaluated. Scientific judgement should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

## 5. Complaints

The person responsible for handling the complaints and deciding the measures to be taken should be qualified by education and/or experience in the specific features of the quality control of herbal medicines.

There are basically two types of complaints, product quality complaints and adverse reactions/events. The former 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 details 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. To address the latter complaint, reports of any adverse reaction/event should be maintained in a separate register in accordance with national and international requirements. Investigation should be conducted to find if the adverse reaction/event is due to quality problem and whether such reactions/events are already reported in the literature or it is a new observation. In either case, complaint records should be reviewed regularly for indication of specific or recurring problems requiring special attention and possible recall of marketed products. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems deals with specific issues relating to adverse reaction and adverse events on herbal medicines (10).

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

The product recall procedure should be related to and depends very much on the national regulation. A standard operating procedure (SOP) should be included for storage of recalled herbal medicinal products in a secure segregated area, complying with the requirements specified under the subtitle 12.1 *Storage areas*, while their fate is decided.

## 7. Contract production and analysis

The contract partner should have adequate premises and equipment for the GMP production of herbal medicines. Validated methods should be applied for cleaning 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 separated from those where the plant raw material will be cut or powdered to be used in the preparation of medicines.

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

#### 8. Self-inspection

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

#### 9. Personnel

For general guidance in relation to personnel involved in the manufacture of medicinal products refer to the parent guide (8).

The release of herbal medicines should be under the authority of 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.

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

#### 10. Training

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

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

#### 11. Personal hygiene

Personnel entrusted with 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 regarding their hygiene control. The personnel should be required to be without infectious diseases, or skin diseases. Documented procedures listing the basic hygienic requirements should be made available.

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 through the whole procedure from plant processing and product manufacturing.

## 12. Premises

As a general principle, premises should be designed, located, constructed, adapted and maintained to suit the GMP operations to be carried out (8).

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.

### *12.1 Storage areas*

Storage areas should be well organized and kept in order. Special attention should be paid to the cleanliness and good maintenance. Any accidental spillage should be cleaned up immediately using cleaning methods which minimize the risk of cross contamination of other materials and should be reported.

The set up of storage areas depends mostly on the type of materials stored. The areas should be well labeled and storing conditions must be in a way to avoid any risk of cross-contamination. A quarantine area should be identified for all incoming herbal materials.

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.

In order to protect it and reduce the risk of pest attacks, storage time of any herbal material in unpacked form should be kept at the shortest possible time.

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

In the case of bulk storage, in order to reduce the risk of mould formation or fermentation it is advisable to use aerated rooms or containers using natural or mechanical aeration/ventilation. These areas should also be equipped in such a way as to give protection against the entry of insects or other 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.

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

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.

Herbal materials including raw herbal materials should be kept in dry area protected from moisture and allow it to keep the principle of “first in and out” (FIFO).

## 12.2 *Production areas*

Production areas should comply with the general requirements of the GMP principles (8). As a rule, campaign work in their processing is necessary. However, if feasible, use of dedicated premises is encouraged. Moreover, taking the special nature of the production of herbal medicines into account, special attention should be given to processing products that generate dust. When heating or boiling of the materials is necessary, suitable air exhaustion mechanism should be employed to prevent accumulation of the unintended fumes and vapours. 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 system to achieve the desired differential pressure and net airflow.

## 13. Equipment

Since processing of herbal materials may generate dust or material which can be easily subject of pest-infestation or microbiological contamination and cross contamination, cleaning of equipment is particularly important.

Vacuum or wet cleaning methods are to be preferred. If wet cleaning is applied, the equipment should be dried immediately after cleaning in order to avoid the growth of microorganisms. Compressed air and brushes should be used with care and avoided if possible, as they increase the risk of product contamination.

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 advised not to come into direct contact with chemicals and contaminated material. If it is unavoidable, special consideration must be given to their cleaning as wooden material may “keep” smell and colour and is easily contaminated.

## 14. Materials

All incoming herbal materials should be quarantined and stored under the appropriate conditions taking into account the degradable character of herbal materials and herbal preparations.

For fumigation, only permitted substances should be used and allowable limits for their residues along with instrumental specifications should be set, according to the national regulations.

### 14.1 *Reference samples and standards*

In the case of herbal medicines, the reference standard may be a botanical sample of the herbal material, a sample of the herbal preparation, e.g. extract, a chemically defined substance e.g. a known active constituent or a marker substance or a known impurity. The reference standard should have the quality appropriate to its purpose. If the herbal medicines 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 (if the whole medicinal plant is e.g., 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

The general principles for documentation are set out in the parent guidelines (8).

### *15.1 Specifications*

The specifications for starting herbal 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 the 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 their collection or agricultural production. For instance, the selection of seeds, conditions of cultivation and harvesting represent an important aspect in producing a reproducible quality of herbal medicines (7). Their characterization (which includes also 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 specifications to be established, which are both comprehensive and relevant.

For this reason, apart from the data called for in (8), the specifications for herbal materials should as far as possible include, as a minimum, the following:

#### *Herbal materials*

- The family and botanical name of the plant used according to the binomial system (genus, species, variety and the authority, which is the reference to the originator of the classification, e.g. Linnaeus). It may be appropriate to add also 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, time period and conditions of harvesting (e.g. extreme weather), collection procedures, collection area and brand, quantity and date of pesticide used, as required by (7).
- Whether the whole plant or only a part is used. In the latter case, which part of plant is used and its state, e.g. whole, reduced etc. With dried plant material the drying system should be specified, if applicable.
- A description of the plant material based on visual (macroscopical) and/or microscopical examination.
- Suitable identification 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.
- 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 extractive, moisture/water content and loss on drying (with due respect to 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, biological fingerprints such as induced fluorescent markers, etc.)

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

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

Starting materials derived from or comprising genetically modified organisms should comply with existing national/international regulations and labelled as such. Chemical protection of herbal materials should be used in accordance with national and/or international regulations (7).

Expression of qualitative and quantitative particulars of the active ingredients or constituents with known therapeutic activity in herbal materials and herbal preparations should be given as required by the subtitle *17.5 Labeling*.

#### Finished herbal products

- Microbiological contamination and tests for other toxicants.
- Uniformity of weight (for tablets, single-dose powders, suppositories, herbal tea in sachets and capsules, etc.), 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 are identified and the adequate analytical methods are available.
- Limit tests for residual solvents.

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. If such substances are not known, 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.

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.

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.

#### Herbal preparations

The specification of herbal preparations consists, depending on the case, the relevant items of the specification of herbal materials or finished herbal products outlined above.

#### *15.2 Processing instructions*

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

Drying conditions chosen should be appropriate to the type of plant materials 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, flower etc). Drying directly with exposure to sunlight, if not specifically contraindicated, is possible but drying on the ground should be avoided. Where the plant should be processed fresh and without drying the reasons and criteria determining the use of fresh material should be stated.

For the production of processed extracts, the instructions should specify details of any vehicle or solvent that may be used, the times and temperatures to be observed during extraction, and any concentration stages and methods that may be required.

The permissible environmental conditions e.g. temperature, humidity, cleanliness should be stated.

Any treatment, such as fumigation, used to reduce fungal/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 along with instrumental specifications.

Blending and adjustment/standardization (to reach defined content(s) of pharmacologically active constituent(s) in the latter case) steps should be clearly documented.

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

#### 16. Good practices in production

In order to ensure not only quality, but also safety and efficacy of complex products of biological origin, such as herbal medicines, it is essential that their production is clearly defined.

### *16.1 Selection of the first production step covered by these guidelines*

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 where the application of these guidelines start should be clearly designated. The rationale of this designation should be given and documented. Guidance is provided below. However, e.g. for extraction, fermentation, purification etc. this rationale should be established on a case-by-case basis.

- Collection/cultivation and/or harvesting of medicinal plant should follow other relevant guidance such as the WHO or a national guidelines on Good Agriculture and Collection Practices (GACP) for medicinal plants (7). If not available, these guidelines should refer.
- Generally, post harvest processing including primary cutting are (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 recognition 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 of comminuted or powdered herbs exclusively, 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 post harvesting processing.
- In the case of finished herbal products manufactured by fermentation, application of GMP should cover any production step following primary cutting and comminuting. Particularly attention should be given to the introduction of the cells from the cell bank into fermentation process.

### *16.2 General considerations*

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

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, applied for production of other pharmaceutical substances may not be applicable to processing of herbal materials. Specific, and detailed requirements should be developed in respect of microbial contamination of equipment, air, surfaces, and personnel, also for rest rooms, utilities, ancillary and supporting systems (water, compressed air etc.).

Care should be taken to choose methods for cleaning depending on the characteristics of herbal materials. Washing dried herbal materials with water, as a rule, is not appropriate. When their cleaning is necessary, air duster/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. suspected coliform bacteria), it should be limited minimum.

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

If time limits are specified in the master production instruction, these time limits should be met to ensure the quality of intermediates and finished products. The less the constituents responsible for the therapeutic activity are known, the more this rule should be obeyed. Such time limits, however, may be inappropriate when processing to a target value (e.g. drying to a predetermined specification) because completion of processing steps are determined by in process sampling and testing.

### *16.3 Mixing of batches and blending*

Herbal medicines with constituents of known therapeutic activity are often standardized (i.e. adjusted to a defined content of such constituents). It should be documented how such standardization is achieved. If another substance is used for these purposes, it is necessary to specify as a range the quantity that can be added. Blending different batches of a specific herbal material (e.g. before extraction) or by mixing different lots of similar herbal preparations could also be acceptable. Records for traceability should be maintained. The blending process should be adequately controlled and documented and the blended batch should be tested for conformity to establish specifications where appropriate.

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

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

Where 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.

Expiry date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

## 17. Good Practices in quality control

### *17.1 General*

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

The quality control of the herbal material, herbal preparations and finished herbal products should establish their quality but does not imply the control of the whole composition.

### 17.2 Sampling

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

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

### 17.3 Testing

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 comprises instruments to perform the tests described in (6). Moreover, each country should develop this basic requirement for technical equipment further, according to the country's needs.

Herbal material, herbal preparations (including extracts) and finished herbal products fall into the following categories:

- a) the active constituents are identified, may be quantified as such;
- b) the main group of components which contribute to the activity (i.e. the constituents with known therapeutic activity) known and can be quantified as total (e.g. essential oils) or as calculated to a substance belonging 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/feasible.

Identification methods may be based on

- physical and, if applicable, macroscopic (organoleptic) and microscopic tests,
- chromatographic procedures (TLC, HPLC, HPTLC, GLC,), spectral techniques (UV-VIS, IR, NMR, MS) and/or
- chemical reactions.

The identification test methods should be specific for the herbal material, herbal preparation of finished herbal products and optimally should be capable of discriminating between the required herbal material and potential substitutes/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 in the labeling. For groups c) the analytical procedure should be based on characteristic constituents, if any.

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

Quantitative determination of known active components in case of groups a) and b) as well as markers in group c) is necessary.

Development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products should be in line with the subtitle *15.1 Specifications*. Tests and quality requirements that are characteristic to the given analyte should be selected.

Particularly for herbal materials that fall into 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. It should be exercised with care, however, for every delivery of herbal materials and every batch of herbal preparations (including extracts) will have slightly different chromatograms/fingerprints due to differences of chemical compositions caused by intrinsic or extrinsic factors.

#### *17.4 Stability studies*

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

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, since 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 in most of the cases will not be sufficient. It is chromatography that allows tracing changes which may happen in the course of 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 (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.

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

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

To determine the shelf life of finished herbal products, strong emphasis should also be placed on other test listed under the subtitle *15.1 Specifications*, such as moisture content, microbial contamination and general dosage form control tests.

The stability of preservatives and stabilizers should be monitored. When these are not present in the formulation, alternative tests should be provided to ensure that the product is shelf-preserving over its shelf-life.

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

Normally the first three commercial production batches should be placed on 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 frequency of re-testing depends on the characteristic of the herbal medicinal products and should be determined on a case by case basis.

The protocol for on-going stability studies should be documented. This would normally involve one batch per year being placed on a stability programme.

#### 17.5 Packaging materials and labeling

All packaging materials like bottles and other packaging materials should be stored properly. Controls on the issue and use of these packaging materials should be adequately exercised so as to avoid issue of incorrect labels and cartons. All containers and closure should be thoroughly cleaned and dried before packing the products.

There should be adequate information on the label (or in package insert) informing 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.

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 it is not possible, at least the main ingredients should be stated in the label while the full qualitative composition could appear in the package insert.

Expression of qualitative and quantitative particulars of the active ingredients in herbal materials and herbal preparations should be given in the following ways:

1. For herbal materials and herbal preparations consisting of comminuted or powdered herbal materials:
  - (a) the quantity of the herbal material must be stated; or the quantity of the herbal material/herbal preparation should be stated if constituents with known therapeutic activity are unidentified; 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>
Valerianae radix	900 mg

(b)

<i>Name of the active ingredient or active herbal materials</i>	<i>Quantity of constituent</i>
---	--------------------------------

Sennae folium	415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B
---------------	---

2. 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 unidentified (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 these 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>
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
<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>
Sennae folium	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

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

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. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Thirty-second report. Geneva, World Health Organization, 1992:14-59 (WHO Technical Report Series, No. 823).
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, 1996:109-113, Annex 8 (WHO Technical Report Series, No. 863).
3. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Vol. 2. World Health Organization, Geneva 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, 1996:178-184, Annex 11 (WHO Technical Report Series, No. 863). These guidelines were reproduced in *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Vol. 1. World Health Organization, Geneva 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. Good Manufacturing Practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Thirty-seventh report. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908).
9. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Vol. 2, Updated edition, World Health Organization, Geneva, 2004.
10. *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems*, World Health Organization, Geneva, 2004