



FOOD AND DRUGS AUTHORITY

GUIDELINES FOR CONDUCTING cGMP INSPECTION OF HERBAL MANUFACTURING FACILITIES LOCATED IN GHANA

Adapted from WHO guidelines on Good Manufacturing Practices (GMP) for
Herbal Medicines

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TABLE OF CONTENTS

INTRODUCTION	1
General	1
Glossary	2
1. Quality assurance in the manufacture of herbal medicines	
8	
2. Good manufacturing practice for herbal medicines	
8	
3. Sanitation and hygiene	
8	
4. Qualification and validation	
8	
5. Complaints	
9	
6. Product recalls	
9	
7. Contract production and analysis	
9	
8. Self-inspection	
10	
9. Personnel	
10	
	General
.....	10
Key personnel	10
10. Training	11
11. Personal hygiene.....	11
12. Premises	11
General	
11	
Ancillary areas	
12	
Storage areas	12
Production areas	13

General	13
Processing operations	15
Packaging operations	16
13. Equipment	18
14. Materials	18
Reference samples and standards	18
15. Documentation	19
Specifications	20
Processing instructions	23
General	19

ii

Documents required	20
Labels	20
16. Good practices in production	
24 General considerations	
24	
Mixing of batches and blending	25
17. Good practices in quality control	
26 General	
26 Sampling	
26 Testing	
26 Stability studies	
28	
Packaging materials and labelling	29
REFERENCE	32

INTRODUCTION

This is a guidance to applicants who wish to submit application to the Food and Drugs Authority Ghana for the cGMP inspection of their Herbal medicine manufacturing facility. The document is an adapted version of the WHO guidelines on Good Manufacturing Practices (GMP) for herbal medicines.

The FDA recognizes the fact that quality of herbal medicines directly affects their safety and efficacy. 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.

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, the FDA Ghana has committed to this guideline for the quality assurance and control of herbal medicines.

It is therefore important for applicants to adhere to the detailed requirements of this guidelines if their herbal manufacturing facilities ought to be approved by the FDA Ghana.

It is expected that this guideline will support applicants to adequately go through the process of licensing of their herbal manufacturing facilities with the FDA Ghana.

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 product

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

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

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).

authorized person

The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

batch number (or lot number)

A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product

Any product that has completed all processing stages up to, but not including, final packaging.

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

clean area

An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

consignment (or delivery)

The quantity of a herbal product(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

critical operation

An operation in the manufacturing process that may cause variation in the quality of the herbal medicinal product.

cross -contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

finished product

A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in -process control

Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product

Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

manufacture

All operations of purchase of materials and products, production, quality control, release, storage and distribution of herbal medicinal products, and the related controls.

Manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of herbal medicinal products.

marketing authorization (product licence, registration certificate)

A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record

A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material

Any material, including printed material, employed in the packaging of a herbal medicine, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

production

All operations involved in the preparation of a herbal product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

qualification

Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word —validation¹¹ is sometimes extended to incorporate the concept of qualification.

quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that herbal medicinal are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

quality control

Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

quarantine

The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

reconciliation

A comparison between the theoretical quantity and the actual quantity.

recovery

The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

reprocessing

Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and pre-approved as part of the marketing authorization.

reworking

Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

self -contained area

Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

specifications

A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material

Any substance of a defined quality used in the production of a herbal medicine, but excluding packaging materials.

validation

Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

blending

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

constituents with known therapeutic activity

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

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 productl 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

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

medicinal plant materials – see *herbal materials therapeutic activity*

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses, improvement of symptoms of illnesses, as well as beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being.

1. Quality assurance in the manufacture of herbal medicines

The control of starting materials, storage and processing is key to quality assurance of herbal medicines. In addition, 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 adds up to the quality assurance process. For this reason, an appropriate quality assurance system should be applied in the manufacture of herbal medicines.

2. Good manufacturing practice for herbal medicines

2.1 The first critical step of their production where the application of GMP starts should be clearly designated. This is of particular importance for those products which consist solely of comminuted or powdered herbal materials.

3. Sanitation and hygiene

- 3.1** Ensure a high level of sanitation and hygiene during manufacture.
- 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** The written procedure should specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria as well as measures to ensure consistency in quality, efficacy and safety from batch to batch.
- 4.2** 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 and reported to the FDA Ghana in accordance with its guidelines for reporting adverse reactions (**FDA/SMC/SMD/GLRAR/2013/01**). 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.

- 5.5** The Food and Drugs Authority Ghana 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** There should be a standard operating procedure (SOP) for storage of recalled herbal medicines in a secure segregated area.

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. Establish adequate cleaning for the equipment and premises carefully before using them to produce different herbal medicinal, food or cosmetic products.

- 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.

- 7.3** The contract manufacturing facility of the contract acceptor intended to be used for the contract manufacturing process must be licensed by the FDA Ghana.

8. Self-inspection

- 8.1** At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines. Self-inspection should be conducted at least twice a year to cover all the areas of production.

9. Personnel

General

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

- 9.2** Responsible staff should have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities. Its duties may be delegated to designated deputies with a satisfactory level of qualifications. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.
- 9.3** All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instruction, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high quality standards.
- 9.4** Steps should be taken to prevent unauthorized people from entering production, storage and QC areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

- 9.5** Key personnel include the heads of production, the head(s) of quality unit(s) and the authorized person. The quality unit(s) typically comprise the quality assurance and quality control functions. In some cases, these could be combined in one department. The authorized person may also be responsible for one or more of these quality unit(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality unit(s) should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.
- 9.6** The release of herbal medicines should be authorized by a person who has been trained in the specific features of the processing and quality control of herbal materials, herbal preparations and finished herbal products.
- 9.7** 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. As a general principle, premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to *the guidelines as follows; G eneral*

- 12.1** The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- 12.2** Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid crosscontamination and facilitate cleaning.
- 12.3** Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.
- 12.4** Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- 12.5** Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.
- 12.6** Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.
- 12.7** Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the herbal products during their manufacture and storage, or the accurate functioning of equipment.

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

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

12.10 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.

Ancillary areas

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

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

12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

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

Storage areas

12.15 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.

12.16 The set-up of storage areas depends on the type of materials stored. The areas should be well labelled and materials stored in such a way as to avoid any risk of

cross-contamination. An area should be identified for the quarantine of all incoming herbal materials.

12.17 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.

12.18 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.

12.19 Incoming fresh herbal materials should be processed, unless specified otherwise, as soon as possible and should be stored appropriately.

12.20 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.

12.21 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.

12.22 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.

12.23 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

12.24 Production areas should comply with the general requirements of *WHO good manufacturing practices for pharmaceutical products stated as follows:*

12.25 Principle; Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

12.26 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution

should be done in accordance with written procedures or instructions and, where necessary, recorded.

12.27 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be recorded in writing by a designated person, with the involvement of the quality control department, when appropriate.

12.28 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

12.29 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or crosscontamination.

12.30 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases it may be useful to record also the name of the previous product that has been processed.

12.31 Access to production premises should be restricted to authorized personnel.

12.32 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of other products such as food.

12.33 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix-up).

Prevention of cross -contamination and bacterial contamination during production

12.34 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

12.35 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies

with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

12.36 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:

- a. carrying out production in dedicated and self-contained areas
- b. conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
- c. providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
- d. minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
- e. wearing protective clothing where products or materials are handled;
- f. using cleaning and decontamination procedures of known effectiveness;
- g. using a —closed system— in production;
- h. testing for residues;
- i. using cleanliness status labels on equipment.

12.37 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

12.38 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

Processing operations

12.39 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

12.40 Any necessary in-process controls and environmental controls should be carried out and recorded.

12.41 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

12.42 Time limits for storage of equipment after cleaning and before use should be stated and based on data.

12.43 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

12.44 Any significant deviation from the expected yield should be recorded and investigated.

12.45 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

12.46 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

12.47 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

12.48 Repair and maintenance operations should not present any hazard to the quality of the products.

Packaging operations

12.49 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

12.50 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

12.51 The name and batch number of the product being handled should be displayed at

each packaging station or line.

12.52 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

12.53 The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

12.54 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, inprocess control checks should be performed more frequently.

12.55 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

12.56 Regular on-line control of the product during packaging should include at least checks on:

- a. the general appearance of the packages;
- b. whether the packages are complete;
- c. whether the correct products and packaging materials are used;
- d. whether any overprinting is correct;
- e. the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

12.57 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.

12.58 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.

12.59 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

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.

- 12.60** 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.

- 13.4** A Planned preventative maintenance programmes for equipment should be well documented and followed. These should factor the calibration of equipment where required.

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. The source of all raw materials for production shall well documented (i.e. from the wild, self-cultivated, local vendors, imported).

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

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 where applicable.

15. Documentation

15.1 The general principles for documentation are set out as follows:

Principle. Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a herbal product for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. **General**

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

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

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

15.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

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

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

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of herbal products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

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

Documents required Labels

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

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

- a. the name of the herbal product;
- b. a list of the active ingredients (if applicable), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
- c. the batch number assigned by the manufacturer;
- d. the expiry date in an uncoded form;
- e. any special storage conditions or handling precautions that may be necessary;
- f. directions for use, and warnings and precautions that may be necessary;

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

15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

Specifications

15.13 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.

15.14 The specifications for herbal materials should as far as possible include, as a minimum, the following information:

15.15 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).

1. 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.
2. A description of the plant material based on visual (macroscopic) and/or microscopic examination.

3. 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.
4. Details of the assay, where appropriate, of active constituents or markers.
5. 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).
6. 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.
7. Tests for toxic metals and for likely contaminants, foreign materials and adulterants.
8. Tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest-infestations, radioactivity and their acceptable limits.
9. Other appropriate tests (e.g. particle size, swelling index and residual solvents in herbal preparations and biological fingerprints such as induced fluorescent markers).

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

15.17 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.

15.18 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 the relevant regulations of Ghana.

15.19 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 17.26 (labelling).

15.20 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.

15.21 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.

15.22 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.

15.23 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.

15.24 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

15.26 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.

15.27 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.

15.28 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.

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

15.30 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.

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

15.32 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.

x 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.

- x 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.
- x When herbal extracts are used, the principles of these guidelines should apply to any production step following postharvest processing.
- x 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^{ll} 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

General

17.1 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.

17.2 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.

Sampling

17.3 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.

17.4 Further advice on sampling and visual inspection could be obtained in the WHO document *Quality control methods for medicinal plant materials*.

Testing

17.5 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 material*.

17.6 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.

17.7 Identification methods may be based on:

- x physical and, if applicable, macroscopic (organoleptic) and microscopic tests;
- x chromatographic procedures (TLC, HPLC, HPTLC or gas-liquid

chromatography (GLC)), spectrometric techniques (ultraviolet-visible (UV VIS), IR, nuclear magnetic resonance (NMR), MS); and/or x chemical reactions.

- 17.8 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 —all and —bll should be capable of detecting the said active ingredients and at least the main ingredients should be stated on the label. For group —cll, the analytical procedure should be based on characteristic constituents, if any.
- 17.9 Reference samples of herbal materials should be made available for use in comparative tests, e.g. visual and microscopic examination and chromatography.
- 17.10 Quantitative determination of known active components for members of groups —all and —bll and of markers for members of group —cll is necessary.
- 17.11 The development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products should be in line with specification spelled out in this document. Tests and quality requirements that are characteristic of the given analyte should be selected.
- 17.12 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.

Stability studies

- 17.13 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.
- 17.14 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.

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

17.16 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.

17.17 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.

17.18 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 selfpreserving over its shelf-life.

17.19 Samples used for stability studies should be stored in the containers

17.20 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.

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

Packaging materials and labelling

17.22 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.

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

17.24 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.

17.25 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.

17.26 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 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</i>	<i>Quantity of constituent</i>
------------------------------------------------	--------------------------------

<i>plant materials</i>	
<i>Sennae folium</i>	415–500 mg, corresponding to 12.5 mg hydroxyanthracene glycosides, Calculated as sennoside

x 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).

(a)

Name of the active substance or active herbal material	Quantity of constituents
<i>Valerianae radix</i>	25mg dry ethanolic (96% V/V) Extract (8:1) or 125mg ethanolic (96% v/v) Extract equivalent to 1000mg <i>valerianae radix</i>
Other ingredients	
Dextrin	20-50mg

(b)

Name of the active substance or active herbal material	Quantity of constituents
<i>Sennae folium</i>	100-130mg dry ethanolic (96% V/V) Extract (8:1), corresponding to 25mg of hydroxyanthracene glycosides calculated as sennoside B
<i>Other ingredients</i>	
Dextrin	20-50mg

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

17.28 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.

REFERENCE

WHO (2007). WHO updated supplementary guidelines on good manufacturing practices (GMP) for herbal medicines.

WHO good manufacturing practices (GMP): main principles for pharmaceutical products