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Certification scheme for medicinal plant produce — Part 4: Good manufacturing practices (GMP) for herbal medicines

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Foreword

The African Regional Organisation for Standardisation (ARSO) is an African Intergovernmental organization made of Member States of the United Nations Economic Commission for Africa (UNECA) and the African Union (AU). One of the fundamental mandates of ARSO is the establishment of a conformity assessment system to promote the quality of African goods and services as a means of facilitating intra-African trade as well as accessing global markets.

The ARSO Conformity Assessment Programme (ACAP) is supported by a coherent set of documents which are developed under the auspices of the ARSO Conformity Assessment Committee (ARSO CACO) which comprises experts from Member States. Member States participate in the committee on a voluntary basis and the documents developed follow the principles and procedures for the development of African Standards outlined in the African Standards Harmonization Model (ASHAM) with the exception of the stages and voting thresholds. Being conformity assessment instruments, ACAP documents are subject to dynamic adaptations which must timeously respond to changes in the conformity assessment fields.

ACAP documents will be revised on a flexible basis to fit in with changes in global conformity assessment systems.

ARSO Central Secretariat
International House 3rd Floor
P. O. Box 57363 — 00200 City Square
NAIROBI, KENYA

Tel. +254-20-2224561, +254-20-3311641, +254-20-3311608
E-mail: arso@arso-oran.org
Web: www.arso-oran.org

ARSO Central Secretariat
International House 3rd Floor
P.O. Box 57363 — 00200 City Square
NAIROBI, KENYA

Tel: +254-20-2224561, +254-20-3311641, +254-20-3311608

E-mail: arso@arso-oran.org
Web: www.arso-oran.org

Introduction

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

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

The core requirements for GMP for herbal medicines are common to GMP for pharmaceutical products.

There is no doubt that GMP is a key step in ensuring the safety and efficacy of herbal medicines. However, meeting GMP requirements requires investment from manufacturers and this may be especially difficult for small manufacturers. Investing in GMP may increase production costs, leading to an increase in the price of the final product. This will impact on the affordability of the medicines. These certification requirements have been tailored to provide a maturity transition model which starts with minimum requirements and gradually increase with the profile of the manufacturer’s expansion.

Certification scheme for medicinal plant produce — Part 4: Good manufacturing practices (GMP) for herbal medicines

1 Scope

The purpose of this certification document is to outline steps which should be taken, as necessary and appropriate, by manufacturers of traditional medicines with the objective of ensuring that their products are of the intended quality, safety and nature.

2 Normative references

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

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

ARS 56, *Pre-packaged foods — Labelling*

ARS 950, *African Traditional Medicine — Terms and terminology*

ARS 951, *African Traditional Medicine — Good manufacturing practices (GMP) for herbal medicines*

ARS 952, *African Traditional Medicine — Guidelines on good agricultural and collection practices (GACP) for medicinal plants*

ARS 955, *African Traditional Medicine — Technical guidelines for safety, efficacy and quality of raw materials and herbal medicines*

ISO/IEC 17000, *Conformity assessment — Vocabulary and general principles*

ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories*

3 Terms and definitions

For the purpose of this document the terms and definitions in, ARS 950, ARS 951, ISO/IEC 17000 and the following standards apply.

3.1
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).

3.2
good manufacturing practice (GMP)
a manufacturing practice is considered ‘‘good’’ if (Willig, 2000):
(i) It is feasible for manufacturers to implement; (ii) It contributes to ensuring the safety, quality, or purity of the drug product; (iii) The value of the contributions or added assurance exceeds the cost in money or other burdens of implementing or continuing the practice.

3.3
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.

3.4
herbal medicines
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

3.5
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

3.6
herbal preparations
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.

3.7
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*).

3.8
markers
chemically defined constituents of a herbal material utilized for control purposes. They may or may not contribute to the clinical efficacy. When they contribute to the clinical efficacy, however, evidence that they are solely responsible for the clinical efficacy may or may not be available. Markers are generally employed when constituents of known therapeutic activity are not known or are not clearly identified, and may be used to identify the herbal material or preparation or calculate their quantity in the finished product.

3.9
medicinal plant
Medicinal plants are plants (wild or cultivated) used for medicinal purposes.

3.10
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.

4 Quality assurance in the manufacture of herbal medicines

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

5 Good manufacturing for herbal medicines

5.1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as

required by the marketing authorization. GMP are aimed primarily at diminishing the risks inherent in any herbal production. Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, false labels being put on containers. Under GMP:

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

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

(c) all necessary resources are provided, including:

  (i) competent personnel;

  (ii) adequate premises and space;

  (iii) suitable equipment and services;

  (iv) appropriate materials, containers and labels;

  (v) approved procedures and instructions;

  (vi) suitable storage and transport;

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

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

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

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

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

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

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

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

5.2 Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, are covered by ARS 952. 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.

6 Requirements of a GMP

6.1 Components of a GMP

GMP requires that the manufacturing process is fully defined before being initiated and all the necessary facilities are provided. In practice, personnel must be adequately trained, suitable premises and equipment used, correct materials used, approved procedures adopted, suitable storage and transport facilities available, and appropriate records made. The essential components of GMP are summarized in Figure 1 (Lund, 1994; Basnet, 2012).

The manufacturing premises of good design and regularly monitored is the most important component. There should be quality control of finished product, raw materials and packaging materials. The equipment of good design is to be considered and all the equipment are required to be maintained properly. There should be a correct choice of cleaning equipment. The staffs should be trained well and should be wearing protective clothing while on work. There should be written procedures for carrying out the operations.

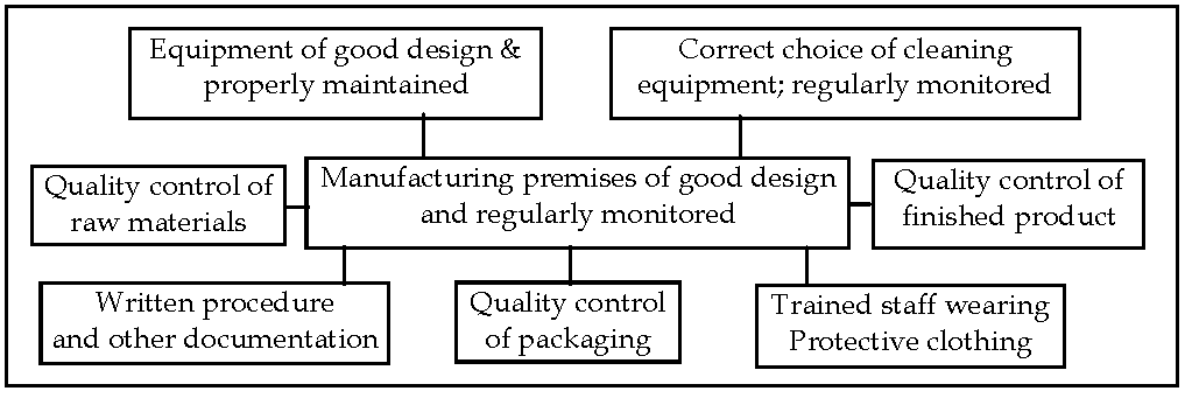

Figure 1 — Components of good manufacturing practice (Lund, 1994; Basnet, 2012)

6.2 Consolidated components of a GMP

This document utilizes the globally recognized consolidated components of good manufacturing practices codified in WHO guidelines (WHO, 2007). The aspects include:

(1) Quality assurance in the manufacture of herbal medicines; (2) Good manufacturing practice for herbal medicines; (4) Sanitation and hygiene; (5) Qualification and validation; (6) Complaints; (7) Product recalls; (8) Contract production and analysis; (9) Self-inspection; (10) Personnel; (11) Training; (12) Personal hygiene; (13) Premises; (14) Equipment; (15) Materials; (16) Documentation; (17) Good practices in production; (18) Good practices in quality control

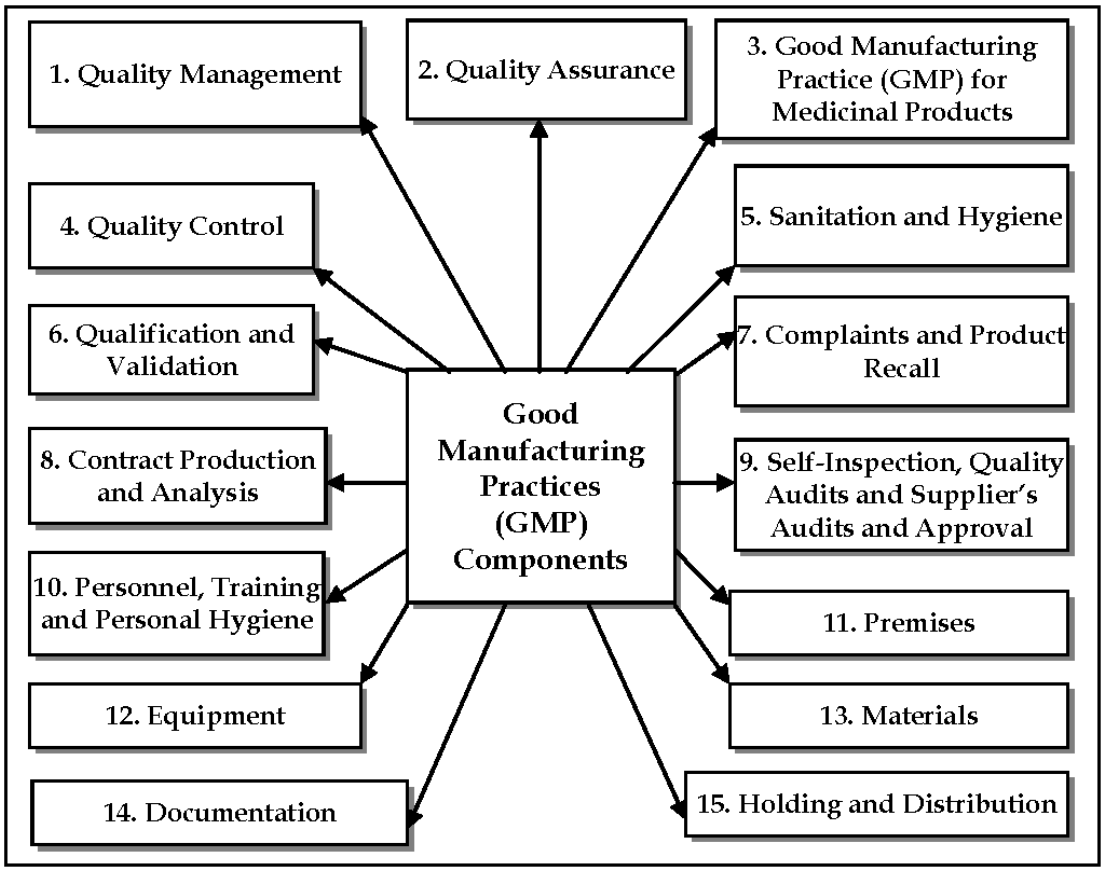

Figure 2 — Consolidated components of good manufacturing practices (Basnet, 2012)

7 Appraisal and assessment

7.1 The requirements stated in Table 1 shall be evaluated to establish that manufacturers comply with those requirements. An appraisal and assessment system has been developed. On evaluation of deficiencies that may appear in evaluation need to be resolved to establish compliance to the requirements. These deficiencies have been classified as:

Critical

When evidence shows that the grower has not complied with requirements in its documentation and implementation and which raises doubts on the operation and practice of GAP calling for an early correction and corrective actions within the time frame.

Major:
When evidence suggests major break down in the implementation in certain elements of the criteria calling for the early corrective actions within a time frame

Minor:

When evidence shows an isolated non-compliance to the GMP criteria and has negligible impact on the operation of the system and its results.

NOTE Multiple Minor NCs with related impact on the operation of the system in one particular area may result in major NC

7.2 To develop a self-assessment method against the criteria, a checklist has been developed and is given in Table 2. This will bring uniformity in evaluation of the system. This also indicates when a violation of a particular criteria leads to critical, major or minor nonconformities.

Table 1 — Checklist for self-assessment for good manufacturing practices (GMP) for medicinal plant produce

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
1	**Quality assurance in the manufacture of herbal medicines**				
1.1	Are quality and GMP considerations incorporated in the production of herbal medicines in a written form? To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities.	O	G	R	R
1.2	Are products designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of hygiene (ARS 53) and labelling (ARS 56)?	R	R	R	R
1.3	Are managerial responsibilities clearly specified in job descriptions?	O	O	R	R
1.4	Are arrangements made for the manufacture, supply and use of the correct starting and packaging materials?	R	R	R	R
1.5	All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out	G	G	R	R
1.6	Are finished products correctly processed and checked, according to the defined procedures?	R	R	R	R
1.7	Products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of herbal products	O	G	R	R
1.8	Satisfactory arrangements exist to ensure, as far as possible, that the herbal products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life	O	O	G	R
1.9	There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system	O	G	R	R
1.10	Deviations are reported, investigated and recorded	O	G	R	R
1.11	There is a system for approving changes that may have an impact on product quality	R	R	R	R
1.12	Regular evaluations of the quality of herbal products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.	O	G	G	R
1.13	All manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing herbal products of the required quality that comply with their specifications	G	G	R	R
1.14	**Resources for implementing GMP** All necessary resources are provided, including (i) appropriately qualified and trained personnel; (ii) adequate premises and space; (iii) suitable equipment and services; (iv) appropriate materials, containers and labels; (v) approved procedures and instructions;	G	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(vi) suitable storage and transport; (vii) adequate personnel, laboratories and equipment for in-process controls				
1.15	Instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided	R	R	R	R
1.16	Operators are trained to carry out procedures correctly.	R	R	R	R
1.17	Records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated	O	G	R	R
1.18	Records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form	G	G	R	R
1.19	The proper storage and distribution of the products minimizes any risk to their quality	R	R	R	R
1.20	A system is available to recall any batch of product from sale or supply	G	G	G	G
1.21	Complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products to prevent recurrence.	G	G	R	R
2	**Primary Processing**				
2.1	**Sorting**				
	All medicinal plant materials are inspected during the primary processing stages of production, and any substandard products or foreign matter eliminated mechanically or by hand, e.g., discoloured, mouldy or damaged materials, soil, stones and any other foreign matter.	R	R	R	R
2.2	**Cleaning**				
	Cleaning of all medicinal plant materials is done appropriately using clean water free from microbial and chemical contaminants	R	R	R	R
2.3	**Drying where applicable**				
2.3.1	The harvested material are unpacked on arrival at the drying facilities. In certain instances the material is not allowed to stand for extended period of time in direct sunlight and is protected from excessive humidity.	R	R	R	R
2.3.2	Buildings used for drying the harvested material are well ventilated and are not used for any other activities.	R	R	R	R
2.3.3	The building is constructed so as to protect the harvested material from birds, insects, and animals.	R	R	R	R
2.3.4	The harvested materials are placed in thin layers, on wire mesh racks standing off the floor to allow free air circulation, and are stirred intermittently to ensure uniform drying and prevent decomposing.	O	O	O	O
2.3.5	Dried harvested materials are inspected to remove discoloured, mouldy, damaged material, soil, stones and any other foreign matter.	R	R	R	R
2.4	**Storage**				
2.4.1	The dried material is packed in clean appropriate containers. Reusable containers are well-cleaned before use. The containers are stored in a clean dry place off the ground, free from pests and inaccessible to animals.	R	R	R	R
2.4.2	Packed dried material is stored in a dry, well ventilated building, with minimal variation in diurnal temperature and with good air ventilation. Shutter and door openings are	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	protected by wire screens to keep out pests and any other animals.				
2.4.3	Packed dried materials are stored in a building with concrete floors; on pallets; away from the wall; well separated from all other materials	O	O	G	R
3	**Sanitation and Hygiene**				
3.1	A high level of sanitation and hygiene is evident and practiced covering personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.	O	G	R	R
3.2	Potential sources of contamination are eliminated through an integrated comprehensive programme of sanitation and hygiene	G	G	R	R
3.3	Water supply to the manufacturing unit is monitored, and/or appropriately to ensure consistency of quality	O	G	R	R
3.4	Waste from the manufacturing unit is disposed of regularly to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste-bins are available, emptied and cleaned as needed, but at least daily.	R	R	R	R
4	**Qualification and Validation**				
4.1	There is a written procedure which specifies critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.	O	G	R	R
4.2	Qualification and validation establishes and provides documentary evidence that: (a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ); (b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ); (c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ); (d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).	O	G	G	R
4.3	A formal change of the control system is established to evaluate the potential effects of any changes on the quality of the herbal medicines, particularly content of the active ingredients. Scientific judgement is used to determine which additional testing and validation studies are appropriate to justify a change in a validated process.	O	O	G	R
4.4	Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, is qualified and validated.	R	R	R	R
4.5	Qualification and validation is an on-going programme following the first implementation and is reviewed annually	O	O	G	R
4.6	The commitment to maintain continued validation status is stated in the relevant company documentation, such as the quality manual or validation master plan.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
4.7	The responsibility of performing validation is clearly defined	R	R	R	R
4.8	Validation studies for GMP are conducted in accordance with predefined and approved protocols	O	O	G	R
4.9	A written report summarizing the results recorded and the conclusions reached is prepared and stored.	O	O	G	G
4.10	Processes and procedures are established on the basis of the results of the validation performed.	O	O	G	G
4.11	There is particular attention paid to the validation of analytical test methods, automated systems and cleaning procedures.	O	O	G	R
5	**Complaints**				
5.1	All complaints and other information concerning potentially defective products is diligently reviewed according to written procedures and corrective action taken	R	R	R	R
5.2	The person responsible for handling complaints and deciding on the measures to be taken to deal with them has appropriate training and/or experience in the specific features of the quality control of herbal medicines	R	R	R	R
5.3	Two types of complaint are recognized: product quality complaints and adverse reactions/events				
5.3.1	The cause of product quality complaints is traced to problems such as faulty manufacture, product defects or deterioration or adulteration of the herbal material. These complaints are recorded in detail and the causes thoroughly investigated (e.g. by comparison with the reference samples kept from the same batch) and there are written procedures to describe the action to be taken.	G	G	R	R
5.3.2	Complaints on adverse reaction/event are entered in a specified register designated by the organization and in accordance with national and international requirements. Investigations are 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. Complaint records are reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products.	G	G	R	R
5.4	Complaints records are regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.	G	G	R	R
5.5	The licensing authority is informed of any complaints leading to a recall or restriction on supply and the records made available for inspection	O	O	G	R
6	**Product Recalls**				
6.1	There is established a system to recall from the market, promptly and effectively, products known or suspected to be defective.	R	R	R	R
6.2	The authorized person is responsible for the execution and coordination of recalls. There is sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.	G	G	R	R
6.3	There are established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations are capable of being initiated promptly down to the required level in the distribution chain.	O	O	G	G

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
6.4	There is a standard operating procedure (SOP) for storage of recalled herbal medicines in a secure segregated area while their fate is decided	O	G	R	R
6.5	All competent authorities of all countries to which a given product has been distributed are promptly informed of any intention to recall the product because it is, or is suspected of being, defective.	R	R	R	R
6.6	The distribution records are readily available to the authorized person, and they contain sufficient information on wholesalers and directly supplied customers to permit an effective recall	G	G	R	R
6.7	The progress of the recall process is monitored and recorded and include the disposition of the product. A final report is issued, including a reconciliation between the delivered and recovered quantities of the products.	G	G	R	R
6.8	The effectiveness of the arrangements for recalls is tested and evaluated from time to time.	R	R	R	R
7	**Contract Production and Analysis**				
7.1	There is a written contract between the contracting party and the contractor which clearly establishes the responsibilities of each party.	R	R	R	R
7.2	Technical aspects of the contract are drawn up by competent persons suitably knowledgeable on the specific characteristics of herbal medicines, including their production and quality control testing.	R	R	R	R
7.3	Contract production and analysis is correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.	R	R	R	R
7.4	The contractor has adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contracting party. Validated methods are applied for cleaning the equipment and premises before using them to produce different herbal medicinal products. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.	R	R	R	R
7.5	All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, are in accordance with the marketing authorization for the product concerned and are agreed by both parties.	R	R	R	R
7.6	The contract permits the contracting party to audit the facilities of the contractor.	R	R	R	R
7.7	In the case of contract analysis, the final approval for release is given by the authorized person.	R	R	R	R
7.8	The contracting party is responsible for assessing the competence of the contractor in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP are followed.	R	R	R	R
7.9	The contracting party provides the contractor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contracting party ensures that the contractor is fully aware	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.				
7.10	The contracting party ensures that all processed products and materials delivered by the contractor comply with their specifications or that the product has been released by the authorized person.	R	R	R	R
7.11	The contractor does not sub-contract a third party for contracted work without the contracting party's prior evaluation and approval of the arrangements. Arrangements between the contractor and any third party ensures that the manufacturing and analytical information is made available in the same way as between the original contracting party and contractor.	R	R	R	R
7.12	The contractor refrains from any activity that may adversely affect the quality of the product manufactured and/or analyzed for the contracting party.	R	R	R	R
7.13	The contract clearly states the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.	R	R	R	R
7.14	The contract describes who is responsible for purchasing, testing and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract states whether or not the contractor takes samples at the premises of the manufacturer.	R	R	R	R
7.15	Manufacturing, analytical, distribution records and reference samples are kept by, or be available to, the contracting party. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect is accessible and specified in the defect/recall procedures of the contracting party.	R	R	R	R
7.16	The contract describes the handling of starting materials, intermediate and bulk products and finished products if they are rejected. It describes the procedure to be followed if the contract analysis shows that the tested product is rejected.	R	R	R	R
8	**Self-Inspection and Quality Audits**				
8.1	There is a procedure for self-inspection documented intended to objectively evaluate the manufacturer's compliance with GMP in all aspects of production and quality assurance.	R	R	R	R
8.2	Written instructions for self-inspection are established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items: (a) personnel; (b) premises including personnel facilities; (c) maintenance of buildings and equipment; (d) storage of starting materials and finished products;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(e) equipment; (f) production and in-process controls; (g) quality control; (h) documentation; (i) sanitation and hygiene; (j) validation and revalidation programmes; (k) calibration of instruments or measurement systems; (l) recall procedures; (m) complaints management; (n) labels control; (o) results of previous self-inspections and any corrective steps taken.				
8.3	**Self-inspection team** There is a self-inspection team appointed by management consisting of experts in their respective fields and familiar with GMP. At least one member of the self-inspection team has expert knowledge of herbal medicines.	O	G	R	R
8.4	**Frequency of self-inspection** The frequency at which self-inspections are conducted is preferably at least once a year and is stated in the procedure.	G	G	G	G
8.5	**Self-inspection report** A report is made at the completion of a self-inspection highlighting: (a) self-inspection results; (b) evaluation and conclusions and (c) recommended corrective actions	R	R	R	R
8.6	**Follow-up action** There is an effective follow-up programme by management which based on evaluation of self-inspection reports and recommended corrective actions as necessary.	R	R	R	R
8.7	**Quality audit** Self-inspection is supplemented with an independent/outside quality audit consisting of an examination and assessment of all or part of a quality system with the specific purpose of improving it.	R	R	R	R
8.8	**Suppliers' audits and approval** The person responsible for quality assurance has responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.	R	R	R	R
8.9	Suppliers are evaluated prior inclusion in the supplier's list considering supplier's history and the nature of the materials to be supplied. Where required, audits are conducted to determine the supplier's ability to comply with GMP standards.	R	R	R	R
9	**Personnel**				
9.1	There is a sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible.	R	R	R	R
9.2	The responsibilities placed on any one individual are not so extensive as to present any risk to quality.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
9.3	All responsible staff have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There are no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer has an organization chart.	R	R	R	R
9.4	All personnel are aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel are motivated to support the establishment and maintenance of high quality standards.	R	R	R	R
9.5	Steps are taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas do not use them as a passageway.	R	R	R	R
9.6	The release of herbal medicines is 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.	R	R	R	R
9.7	Personnel dealing with the production and quality control of herbal medicines have adequate training in the specific issues relevant to herbal medicines.	R	R	R	R
9.8	The manufacturer has key personnel such as the head of production, the head of quality control and the authorized person, preferably on full-time basis and independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.	R	R	R	R
9.9	Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products possess the qualifications of a scientific education and practical experience to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products. Their education includes the study of an appropriate combination of: (a) chemistry (analytical or organic) or biochemistry; (b) chemical engineering; (c) microbiology; (d) pharmaceutical sciences and technology; (e) pharmacology and toxicology; (f) physiology; (g) other related sciences. The personnel also have adequate practical experience in the manufacture and quality assurance of herbal products.	R	R	R	R
9.10	The heads of the production and quality control have some shared, or jointly exercised, responsibilities relating to quality, including, but not to: (a) authorization of written procedures and other documents, including amendments; (b) monitoring and control of the manufacturing environment;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(c) plant hygiene; (d) process validation and calibration of analytical apparatus; (e) training, including the application and principles of quality assurance; (f) approval and monitoring of suppliers of materials; (g) approval and monitoring of contract manufacturers; (h) designation and monitoring of storage conditions for materials and products; (i) performance and evaluation of in-process controls; (j) retention of records; (k) monitoring of compliance with GMP requirements; (l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.				
9.11	The head of the production generally has the following responsibilities: (a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality; (b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation; (c) to ensure that the production records are evaluated and signed by a designated person; (d) to check the maintenance of the department, premises, and equipment; (e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available; (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.	R	R	R	R
9.12	The head of the quality control generally has the following responsibilities: (a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation with their specifications; (b) to evaluate batch records; (c) to ensure that all necessary testing is carried out; (d) to approve sampling instructions, specifications, test methods and other quality control procedures; (e) to approve and monitor analyses carried out under contract; (f) to check the maintenance of the department, premises and equipment;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out; (h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.				
9.13	The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.	R	R	R	R
9.14	The authorized person is also involved in other activities, including the following: (a) implementation (and, when needed, establishment) of the quality system; (b) participation in the development of the company's quality manual; (c) supervision of the regular internal audits or self-inspections; (d) oversight of the quality control department; (e) participation in external audit (vendor audit); (f) participation in validation programmes.	R	R	R	R
9.15	The function of the approval of the release of a finished batch or a product is only delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure.	R	R	R	R
9.16	The person responsible for approving a batch for release always ensures that the following requirements have been met: (a) the marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned; (b) the principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed; (c) the principal manufacturing and testing processes have been validated, if different; (d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records; (e) any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to, and approval by, the drug regulatory authority; (f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations; (g) all necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff; (i) approval has been given by the head of quality control; (j) all relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).				
10	**Training**				
10.1	The personnel 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).	R	R	R	R
10.2	Approved training programmes are available besides basic training on the theory and practice of GMP for newly recruited personnel relevant to the duties assigned to them. Continuing training is also given, and its practical effectiveness periodically assessed. Training records should be kept.	G	G	R	R
10.3	Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, are given specific training	R	R	R	R
10.4	The concept of quality assurance and all the measures which aid its understanding and implementation is fully discussed during the training sessions.	G	G	R	R
10.5	Visitors or untrained personnel are not be taken into the production and quality control areas. Whenever this is unavoidable, they are given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.	R	R	R	R
10.6	Consultant and contract staff are qualified for the services they provide and there are verifiable records on this.	R	R	R	R
11	**Personal Hygiene**				
11.1	All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections also undergo periodic eye examinations.	R	R	R	R
11.2	Personnel entrusted with the handling of herbal materials, herbal preparations and finished herbal products have a high degree of personal hygiene and have received adequate training in maintaining appropriate standards of hygiene. The personnel are not allowed to work if they have infectious diseases or skin diseases. Written procedures listing the basic hygiene requirements are available.	R	R	R	R
11.3	Persons shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products are not allowed to handle starting materials, packaging materials, in-process materials or drug products until the condition is no longer judged to be a risk.	R	R	R	R
11.4	All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.	R	R	R	R
11.5	Personnel are protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	protective clothing such as: suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture.				
11.6	To ensure protection of the product from contamination, personnel wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Reusable are stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.	R	R	R	R
11.7	Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines are not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.	R	R	R	R
11.8	Personal hygiene procedures including the use of protective clothing apply to all persons entering production areas, whether they are temporary or full-time employees or nonemployees, e.g. contractors' employees, visitors, senior managers, and inspectors.	R	R	R	R
12	**Premises**				
12.1	Premises are located, designed, constructed, adapted, and maintained to suit the operations to be carried out.	R	R	R	R
12.2	The layout and design of premises minimizes the risk of errors and permits 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.	R	R	R	R
12.3	Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures are taken to avoid cross-contamination and facilitate cleaning.	R	R	R	R
12.4	Premises are 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.	R	R	R	R
12.5	Premises used for the manufacture of finished products are suitably designed and constructed to facilitate good sanitation.	R	R	R	R
12.6	Premises are carefully maintained, and repair and maintenance operations do not present any hazard to the quality of products.	R	R	R	R
12.7	There are records demonstrating that premises are cleaned and, where applicable, disinfected according to detailed written procedures.	R	R	R	R
12.8	Evidence that electrical supply, lighting, temperature, humidity and ventilation are appropriate and they do not adversely affect, directly or indirectly, either the herbal products during their manufacture and storage, or the accurate functioning of equipment.	R	R	R	R
12.9	Evidence that the premises are designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals.	R	R	R	R
12.10	Evidence that there is a procedure for rodent and pest control.	R	R	R	R
12.11	Evidence that the premises are designed to ensure the logical flow of materials and personnel.	R	R	R	R
	Ancillary areas				

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
12.12	Demonstration that rest and refreshment rooms are separate from manufacturing and control areas.	R	R	R	R
12.13	Evidence that facilities for changing and storing clothes and for washing and toilet purposes are easily accessible and appropriate for the number of users.	R	R	R	R
12.14	Evidence that toilets do not communicate directly with production or storage areas.	R	R	R	R
12.15	Evidence that maintenance workshops are separated from production areas and whenever parts and tools are stored in the production area, they are kept in rooms or lockers reserved for that use.	R	R	R	R
12.16	Evidence that animal houses are well isolated from other areas, with separate entrance (animal access) and air-handling facilities.	R	R	R	R
	Storage areas				
12.17	Evidence that storage areas have sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.	R	R	R	R
12.18	Evidence that storage areas are designed or adapted to ensure good storage conditions: clean, dry, sufficiently lit and maintained within acceptable temperature limits.	R	R	R	R
12.19	Demonstration that where special storage conditions are required (e.g. temperature, humidity) these are provided, controlled, monitored and recorded where appropriate.				
12.20	Demonstration that storage areas are well organized and tidy, clean, well maintained and there is a procedure to immediately clean up accidental spillage to minimize the risk of cross-contamination of other materials.	R	R	R	R
12.21	Evidence that the storage areas are set up depending on the materials stored: they are well labelled and materials stored in such a way as to avoid any risk of cross-contamination.	R	R	R	R
12.22	Evidence that the storage areas are laid out to permit effective and orderly segregation of the various categories of herbal materials stored, and to allow rotation of stock.	R	R	R	R
12.23	Evidence that the duration of storage of any herbal material in unpacked form is kept to a minimum to reduce the risk of pest attacks and deterioration.	R	R	R	R
12.24	Evidence that incoming fresh herbal materials are processed as soon as possible unless specified otherwise. If appropriate, they are stored between 2 °C and 8 °C, whereas frozen materials are stored below –18 °C.	R	R	R	R
12.25	Evidence that where materials are stored in bulk, they are stored in aerated rooms or containers using natural or mechanical aeration and ventilation to reduce the risk of mould formation or fermentation and these areas are equipped in such a way as to protect against the entry of insects or animals, especially rodents.	R	R	R	R
12.26	Evidence that herbal materials stored in fibre drums, bags or boxes are stored off the floor and suitably spaced to permit cleaning and inspection.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
12.27	Evidence that special conditions of humidity and temperature or protection from light are provided, maintained, monitored and recorded for the storage of plants, extracts, tinctures and other preparations.	R	R	R	R
12.28	Evidence that all herbal materials are kept in a dry area protected from moisture and processed following the principle of “first in, first out” (FIFO).	R	R	R	R
	Weighing areas				
12.29	Demonstration that the weighing of starting materials and the estimation of yield by weighing is carried out in separate weighing areas designed for that use.	R	R	R	R
	Production areas				
12.30	Evidence that production areas comply with the general requirements of ARS 951 with the use of the use of dedicated premises being preferred.	R	R	R	R
12.31	Demonstration that adequate precautions are 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 to facilitate cleaning and to avoid cross-contamination.	R	R	R	R
12.32	Demonstration that premises are laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.	O	O	G	R
12.33	Demonstration that there is adequacy of the working and in-process storage space to permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different herbal products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.	O	O	G	R
12.34	Evidence that where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) they are smooth and free from cracks and open joints, do not shed particulate matter, and permit easy and effective cleaning and, if necessary, disinfection.	O	G	R	R
12.35	Demonstration that pipework, light fittings, ventilation points and other services are designed and sited to avoid the creation of recesses that are difficult to clean and are preferably accessible from outside the manufacturing areas for maintenance purposes.	R	R	R	R
12.36	Evidence that drains are of adequate size and designed and equipped to prevent back-flow and where open channels are necessary they are shallow to facilitate cleaning and disinfection.	R	R	R	R
12.37	Evidence that production areas are effectively ventilated, with air control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas are regularly monitored during both production and non-production periods to ensure compliance with their design specifications.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
12.38	Evidence that premises for the packaging of finished herbal products are specifically designed and laid out so as to avoid mix-ups or cross-contamination.	O	O	G	R
12.39	Evidence that production areas are well lit, particularly where visual on-line controls are carried out.	R	R	R	R
	Quality control areas				
12.40	Evidence that quality control laboratories are separated from production areas and areas where biological, microbiological or radioisotope test methods are employed are separated from each other.	R	R	R	R
12.41	Demonstration that laboratories have adequate suitable storage space for samples, reference standards, solvents, reagents and records.	R	R	R	R
12.42	Evidence that laboratories are designed with air supply separate from production areas, and there are different air-handling units for biological, microbiological and radioisotope laboratories.	R	R	R	R
12.43	Demonstration, where necessary, that there is a separate room for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors.	R	R	R	R
13	**Equipment**				
13.1	Demonstration that equipment are located, designed, constructed, adapted, and maintained to suit the operations to be carried out.	R	R	R	R
13.2	Evidence that equipment are installed in such a way as to minimize any risk of error or of contamination 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.	R	R	R	R
13.3	Evidence that fixed pipework are clearly labelled to indicate the contents and, where applicable, the direction of flow.	R	R	R	R
13.4	Demonstration that all service piping and devices are adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.	R	R	R	R
13.5	Evidence that balances and other measuring equipment of an appropriate range and precision are available for production and control operations and are calibrated on a scheduled basis.	R	R	R	R
13.6	Evidence that production equipment are thoroughly cleaned on a scheduled basis.	R	R	R	R
13.7	Evidence that available laboratory equipment and instruments are suited to the testing procedures undertaken.	R	R	R	R
13.8	Evidence that washing, cleaning and drying equipment are chosen and used so as not to be a source of contamination.	R	R	R	R
13.9	Evidence that production equipment do not present any hazard to the products and that parts of the production equipment that come into contact with the product are not reactive, additive, or absorptive to an extent that would affect the quality of the product.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
13.10	Demonstration that defective equipment are removed from production and quality control areas, and this is not possible, they are labelled as defective to prevent use.	R	R	R	R
13.11	Demonstration that closed equipment is used whenever appropriate and where open equipment is used or equipment is opened, precautions are taken to minimize contamination.	R	R	R	R
13.12	Evidence that non-dedicated equipment is cleaned according to validated cleaning procedures between production of different herbal products to prevent cross-contamination	R	R	R	R
13.13	Availability of current and updated drawings of critical equipment and support systems.	R	R	R	R
14	**Materials**				
	General				
14.1	Evidence that the manufacturing plant has an updated register of materials (starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials) the main objective which is to produce finished products for patients' use.	R	R	R	R
14.2	Evidence that that no materials used for operations such as cleaning, lubrication of equipment and pest control, come into direct contact with the product unless, where inevitable, these materials are certified as food grade or other such category	R	R	R	R
14.3	Evidence that all incoming herbal materials are quarantined and stored under appropriate conditions taking into account the degradability of herbal materials and herbal preparations	R	R	R	R
14.4	Evidence that all materials and products are stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-in, first-out rule.	R	R	R	R
14.5	Evidence that the water used in the manufacture of finished herbal products is suitable for its intended use.	R	R	R	R
	Starting materials				
14.6	Evidence that the staff engaged in the procurement of starting materials have a particular and thorough knowledge of the products and suppliers.	R	R	R	R
14.7	There is evidence that only starting materials released by the quality control department and within their shelf-life is used.	R	R	R	R
14.8	Evidence that starting materials are dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.	R	R	R	R
14.9	Evidence that materials dispensed for each batch of the final product is kept together and conspicuously labelled as such.	R	R	R	R
	Packaging materials				
14.10	Evidence that the purchase, handling and control of primary and printed packaging materials is the same as for starting materials.	R	R	R	R
14.11	Demonstration that printed packaging materials are stored in secure conditions so as to exclude the possibility of	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	unauthorized access. Roll-feed labels should be used wherever possible. Cut labels and other loose printed materials are stored and transported in separate closed containers so as to avoid mix-ups.				
14.12	Evidence that packaging materials are issued for use only by designated personnel following an approved and documented procedure.				
14.13	There is evidence that each delivery or batch of printed or primary packaging material is given a specific reference number or identification mark.	R	R	R	R
14.14	Evidence that outdated or obsolete primary packaging material or printed packaging material is destroyed and its disposal recorded.	R	R	R	R
14.15	Evidence that all products and packaging materials are checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.	R	R	R	R
	Intermediate and bulk products				
14.16	Demonstration that intermediate and bulk products are kept under appropriate conditions.	R	R	R	R
14.17	Evidence that intermediate and bulk products purchased as such are handled on receipt as though they were starting materials.	R	R	R	R
	Finished products				
14.18	Evidence that finished products are held in quarantine until their final release, after which they are stored as usable stock under conditions established by the manufacturer.	R	R	R	R
14.19	There is evidence that the evaluation of finished products and the documentation necessary for release of a product for sale are in accordance with the requirements described in Section 17, “Good practices in quality control”.	R	R	R	R
	Rejected, recovered, reprocessed and reworked materials				
14.20	Demonstration that rejected materials and products are clearly marked as such and stored separately in restricted areas.	R	R	R	R
14.21	Evidence that rejected materials and products are either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner under the guidance of the authorized personnel and recorded.				
14.22	Demonstration that the reworking or recovery of rejected products is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved and recorded. A reworked batch should be given a new batch number.	R	R	R	R
14.23	There is evidence of additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated.	R	R	R	R
	Recalled products				
14.24	Demonstration that recalled products are identified and stored separately in a secure area until a decision is taken on their fate.	R	R	R	R

No.	Control criteria	Level of compliance			
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	Returned goods				
14.25	There are records showing that products returned from the market are destroyed unless it is certain that their quality is satisfactory, in which they may be considered for resale or re-labelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure.	R	R	R	R
	Reagents and culture media				
14.26	There are records for the receipt and preparation of reagents and culture media.	R	R	R	R
14.27	Demonstration that reagents made up in the laboratory are prepared according to written and validated procedures and appropriately labelled, indicating the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions.	R	R	R	R
	Reference standards				
14.28	Evidence that whenever official reference standards exist, they are preferably used and only for the purpose described in the appropriate monograph.	R	R	R	R
14.29	There is evidence that secondary or working standards are established by the application of appropriate tests and checks at regular intervals to ensure standardization.	R	R	R	R
14.30	Evidence that reference standards are properly labelled with at least the following information: (a) name of the material; (b) batch or lot number and control number; (c) date of preparation; (d) shelf-life; (e) potency; (f) storage conditions.	R	R	R	R
14.31	Demonstration that all in-house reference standards are standardized against an official reference standard, when available, initially and at regular intervals thereafter.	R	R	R	R
14.32	Evidence that all reference standards are stored and used in a manner that will not adversely affect their quality.	R	R	R	R
	Waste materials				
14.33	There are appropriate provisions for the proper and safe storage of waste materials awaiting disposal.	R	R	R	R
14.34	Evidence that toxic substances and flammable materials are stored in suitably designed, separate, enclosed cupboards, as required by national legislation.				
14.35	Demonstration that waste material is not be allowed to accumulate and is disposed of safely and in a sanitary manner at regular and frequent intervals.	R	R	R	R
	Miscellaneous				
14.36	Evidence that rodenticides, insecticides, fumigating agents and sanitizing materials are not permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.	R	R	R	R
14.37	Evidence that only permitted substances are used for fumigation, cleaning, lubrication of equipment and pest	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	control and allowable limits for their residues together with specifications for the apparatus used are set according to product standards and where possible such materials are of food grade quality				
15	**Documentation**				
15.1	**Principle and Document Control**				
15.1.1	Demonstration of good documentation which defines 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 drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. Such documentation ensures the availability of the data needed for validation, review and statistical analysis.	R	R	R	R
15.1.2	Evidence that documents are designed, prepared, reviewed, distributed they comply with the relevant parts of the manufacturing and marketing authorizations.	G	G	R	R
15.1.3	Evidence that documents are approved, signed and dated by the appropriate responsible persons and are not changed without authorization and approval.	G	G	R	R
15.1.4	Evidence that documents have unambiguous contents: the title, nature and purpose is clearly stated. The reproduction of working documents from master documents do not allow any error to be introduced through the reproduction process.	G	G	R	R
15.1.5	Evidence that documents are regularly reviewed and kept up to date and superseded documents withdrawn and archived for a specific period of time.	G	G	R	R
15.1.6	Where documents require the entry of data, these entries are clear, legible and indelible and sufficient space is provided for such entries.	R	R	R	R
15.1.7	Evidence that any alteration made to a document is signed and dated while permitting the reading of the original information and the rationale for alteration recorded.	G	G	R	R
15.1.8	Records are 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.	G	G	R	R
15.1.9	Evidence that master formulae and detailed standard operating procedures relating to the system in use are available and the accuracy of the records can be checked.	R	R	R	R
15.2	**Labels**				
15.2.1	Labels applied to containers, equipment or premises are clear, unambiguous and in the company's agreed format.	R	R	R	R
15.2.2	All finished products are identified by labelling, bearing at least the following information: (a) the name of the herbal product; (b) a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume); (c) the batch number assigned by the manufacturer; (d) the expiry date in an uncoded form; (e) any special storage conditions or handling precautions that may be necessary;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(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.				
15.2.3	For reference standards, the label and/or accompanying document indicates potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.	R	R	R	R
	Specifications and testing procedures				
15.3	Documented testing procedures are validated in the context of available facilities and equipment before they are adopted for routine testing	R	R	R	R
15.4	Specifications are appropriately authorized and dated, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products and; where appropriate, for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production are included.	R	R	R	R
15.5	Each specification should be approved, signed and dated, and maintained by quality control, the quality assurance unit or documentation centre.	R	R	R	R
15.6	Specifications are reviewed to comply with new editions of the national pharmacopoeia or other official compendia.	R	R	R	R
15.7	Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.	R	R	R	R
	Specifications for starting and packaging materials				
15.8.1	Specifications for starting, primary and printed packaging materials provide, if applicable, a description of the materials, including: (a) the designated name (if applicable, the INN) and internal code reference; (b) the reference, if any, to a monograph; (c) qualitative and quantitative requirements with acceptance limits.	R	R	R	R
15.8.2	Depending on the company's practice, other data may be added to the specification, such as: (a) the supplier and the original producer of the materials; (b) a specimen of printed materials; (c) directions for sampling and testing, or a reference to procedures; (d) storage conditions and precautions; (e) the maximum period of storage before re-examination.	R	R	R	R
15.8.3	Packaging material conform to specifications, and are compatible with the material and/or with the drug product it contains. Evidence that the material is examined for compliance with the specification, and for defects as well as for the correctness of identity markings.	R	R	R	R
15.9	Evidence that documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.	R	R	R	R
15.10	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	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	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.				
15.11	For this reason, in addition to the data called for in (*1*), the specifications for herbal materials should as far as possible include, as a minimum, the following information:	R	R	R	R
	Herbal Materials				
15.12	(a) 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. (b) 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 ARS 952. (c) 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. (d) A description of the plant material based on visual (macroscopic) and/or microscopic examination. (e) 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. (f) Details of the assay, where appropriate, of active constituents or markers. (g) 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). (h) 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.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(i) Tests for toxic metals and for likely contaminants, foreign materials and adulterants. (j) Tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest-infestations, radioactivity and their acceptable limits. (k) Other appropriate tests (e.g. particle size, swelling index and residual solvents in herbal preparations and biological fingerprints such as induced fluorescent markers).				
15.13	Specifications for starting materials (and also of primary or printed packaging materials) should include, if applicable, reference to a pharmacopoeial monograph.	R	R	R	R
15.14	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.	R	R	R	R
15.15	Starting materials derived from or comprising genetically modified organisms should comply with existing national or international regulations and the label should include this information. Chemical protection of herbal materials should be in accordance with national and/or international regulations (*7*).	R	R	R	R
15.16	Qualitative and quantitative information on the active ingredients or constituents with known therapeutic activity in herbal materials and herbal preparations should be given as described in subsection 17.5 (labelling).	R	R	R	R
	Specifications for intermediate and bulk products				
15.17	Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.	R	R	R	R
	Finished herbal products				
15.18	Specifications for finished products should include: (a) the designated name of the product and the code reference, where applicable; (b) the designated name(s) of the active ingredient(s) (if applicable, with the INN(s)); (c) the formula or a reference to the formula; (d) a description of the dosage form and package details; (e) directions for sampling and testing or a reference to procedures; (f) the qualitative and quantitative requirements, with acceptance limits; (g) the storage conditions and precautions, where applicable; (h) the shelf-life.	R	R	R	R
	— 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.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	— 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.				
15.19	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.	R	R	R	R
15.20	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.	R	R	R	R
15.21	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.	R	R	R	R
	Herbal preparations formulae				
15.22	A formally authorized master formula should exist for each product and batch size to be manufactured.	R	R	R	R
15.23	The master formula should include: (a) the name of the product, with a product reference code relating to its specification; (b) a description of the dosage form, strength of the product and batch size; (c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing); (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable; (e) a statement of the processing location and the principal equipment to be used; (f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(g) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures); (h) the instructions for any in-process controls with their limits; (i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions; (j) any special precautions to be observed.				
	Processing instructions				
15.24	The processing instructions should describe the different operations to be performed on the plant material, such as drying, crushing, milling and sifting. They should also include the time and, if applicable, temperatures required in the drying process, and the methods to be used to control fragment or particle size. Instructions on removing foreign matters and other unwanted materials should also be given.	R	R	R	R
15.25	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.	R	R	R	R
15.26	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.	R	R	R	R
15.27	The permissible environmental conditions e.g. temperature, humidity and standard of cleanliness, should be stated.	R	R	R	R
15.28	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.	R	R	R	R
15.29	Steps in the processes of blending and adjustment to reach defined contents of pharmacologically active constituents should be clearly documented.	R	R	R	R
15.30	The rules that apply to the disposal of spent herbal material after processing should also be elaborated.	R	R	R	R
	Packaging instructions				
15.31	Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to: (a) the name of the product; (b) a description of its pharmaceutical form, strength and, where applicable, method of application; (c) the pack size expressed in terms of the number, weight or volume of the product in the final container; (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	and types, with the code or reference number relating to the specifications for each packaging material; (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked; (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations; (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used; (h) details of in-process controls with instructions for sampling and acceptance limits.				
	Batch processing records				
15.32	A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)	R	R	R	R
15.33	Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.	R	R	R	R
15.34	During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations: (a) the name of the product; (b) the number of the batch being manufactured; (c) dates and times of commencement, of significant intermediate stages, and of completion of production; (d) the name of the person responsible for each stage of production; (e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing); (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added); (g) any relevant processing operation or event and the major equipment used; (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained; (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(j) notes on special problems including details, with signed authorization for any deviation from the master formula.				
	Batch packaging records				
15.35	A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.	R	R	R	R
15.36	Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.	R	R	R	R
15.37	The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password: (a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation; (b) the date(s) and time(s) of the packaging operations; (c) the name of the responsible person carrying out the packaging operation; (d) the initials of the operators of the different significant steps; (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls; (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area; (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting; (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person; (i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.	R	R	R	R
	Standard operating procedures (SOPs) and records				
15.38	Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for: (a) equipment assembly and validation;	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	(b) analytical apparatus and calibration; (c) maintenance, cleaning and sanitization; (d) personnel matters including qualification, training, clothing and hygiene; (e) environmental monitoring; (f) pest control; (g) complaints; (h) recalls; (i) returns.				
15.39	There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.	R	R	R	R
15.40	The records of the receipts should include: (a) the name of the material on the delivery note and the containers; (b) the "in-house" name and/or code of material if different from (a); (c) the date of receipt; (d) the supplier's name and, if possible, manufacturer's name; (e) the manufacturer's batch or reference number; (f) the total quantity, and number of containers received; (g) the batch number assigned after receipt; (h) any relevant comment (e.g. state of the containers).	R	R	R	R
15.41	There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.	R	R	R	R
15.42	Standard operating procedures should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.	R	R	R	R
15.43	There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.	R	R	R	R
15.44	The sampling instructions should include: (a) the method of sampling and the sampling plan; (b) the equipment to be used; (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality; (d) the amount(s) of sample(s) to be taken; (e) instructions for any required subdivision of the sample; (f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling; (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
15.45	There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.	R	R	R	R
15.46	The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.	R	R	R	R
15.47	The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.	R	R	R	R
15.48	Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.	R	R	R	R
15.49	There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.	R	R	R	R
15.50	Analysis records should include at least the following data: (a) the name of the material or product and, where applicable, dosage form; (b) the batch number and, where appropriate, the manufacturer and/or supplier; (c) references to the relevant specifications and testing procedures; (d) test results, including observations and calculations, and reference to any specifications (limits); (e) date(s) and reference number(s) of testing; (f) the initials of the persons who performed the testing; (g) the date and initials of the persons who verified the testing and the calculations, where appropriate; (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.	R	R	R	R
15.51	Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.	R	R	R	R
15.52	Records are maintained of the distribution of each batch of a product in order, e.g. to facilitate recalls.	R	R	R	R
15.53	Records are kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.	R	R	R	R
15.54	The use of major and critical equipment and the areas where products have been processed is appropriately recorded in chronological order.	R	R	R	R
15.55	There are written and implemented procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned.	R	R	R	R
16	**Good Practices in Production**				
16.1	Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	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	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.	R	R	R	R
16.3	For medicinal plants — which are either cultivated or collected from the wild, and which may be used in crude form or subjected to simple processing techniques (such as cutting or comminuting) — the first critical step of their production, i.e. where the application of these guidelines starts, should be clearly designated. The rationale for this designation should be stated and documented. Guidance is provided below. However, for processes such as extraction, fermentation and purification, this rationale should be established on a case-by-case basis. — Collection/cultivation and/or harvesting of medicinal plants should follow other relevant guidance such as ARS 952. — Generally, postharvest processing including primary cutting is covered by ARS 952. If further comminuting is carried out in the manufacturing processing, it should be covered by GMP, or by these supplementary guidelines. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of herbal materials, application of these supplementary guidelines may be extended to encompass these steps. — When the active ingredient, as defined in the Glossary, consists exclusively of comminuted or powdered herbs, application of these guidelines starts at the physical processing following primary cutting and comminuting, and includes packaging. — When herbal extracts are used, the principles of these guidelines should apply to any production step following postharvest processing. — In the case of finished herbal products manufactured by fermentation, application of GMP should cover any production step following primary cutting and comminuting. Particular attention should be given to the introduction of cells from a cell bank into the fermentation process.	R	R	R	R
	General considerations				
16.4	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.	R	R	R	R
16.5	Attention should be paid to “classification” of clean area requirements taking into account the possible high degree of initial microbial contamination of herbal materials. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to processing of herbal materials. Specific and	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	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).				
16.6	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.	R	R	R	R
16.7	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.	R	R	R	R
16.8	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.	R	R	R	R
	Mixing of batches and blending				
16.9	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.	R	R	R	R
16.10	Batches should be mixed only if it can be guaranteed that the mixture will be homogeneous. Such processes should be well documented.	R	R	R	R
16.11	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.	R	R	R	R
16.12	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.	R	R	R	R
16.13	The expiry date of the blended batch should be chosen according to the date of manufacture of the oldest batch in the blend.	R	R	R	R
17	**Good Practices in Quality Control**				
17.1	**General**				

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
17.1.1	The personnel of quality control units should have the necessary expertise in herbal medicines to enable them to carry out identification tests and recognize adulteration, the presence of fungal growth or infestations and lack of uniformity in a consignment of herbal materials.	R	R	R	R
17.1.2	The quality control of the herbal material, herbal preparations and finished herbal products should establish their quality but does not imply the control of every single constituent.	R	R	R	R
17.2	**Sampling**				
17.2.1	Because herbal materials are an aggregate of individual plants and/ or different parts of the same plant and thus have an element of heterogeneity, sampling should be carried out with special care by personnel with the necessary expertise.	R	R	R	R
17.2.2	Further advice on sampling and visual inspection is given in ARS 955.	R	R	R	R
17.3	**Testing**				
17.3.1	The identity and quality of herbal material, herbal preparations and of finished herbal products should be tested as described in the *Quality control methods for medicinal plant materials* (*6*). The minimum requirement for the technical equipment is for instruments to perform the tests described in (*6*). Moreover, each country should develop this basic requirement for technical equipment further, according to the country's needs.	R	R	R	R
17.3.2	Herbal material, herbal preparations (including extracts) and finished herbal products can be categorized as follows: (a) the active constituents are identified, and may be quantified as such; (b) the main group of components which contribute to the activity (i.e. the constituents with known therapeutic activity) are known and can be quantified as a total (e.g. essential oils) or calculated using a representative substance belonging to the group (e.g. flavonoids); (c) the former are not identified and/or not quantifiable, but marker substances are; (d) others, where quantification (i.e. specification for a certain quantity of a constituent) is not applicable or feasible.	R	R	R	R
17.3.3	Identification methods may be based on: — physical and, if applicable, macroscopic (organoleptic) and microscopic tests; — chromatographic procedures (TLC, HPLC, HPTLC or gas–liquid chromatography (GLC)), spectrometric techniques (ultraviolet-visible (UV-VIS), IR, nuclear magnetic resonance (NMR), MS); and/or — chemical reactions.	R	R	R	R
17.3.4	The identification test methods should be specific for the herbal material, herbal preparation or finished herbal product and ideally should be capable of discriminating between the required herbal material and potential substitutes or adulterants that are likely to occur. The identification methods used for groups (a) and (b) should be capable of detecting the said active ingredients and at least the main ingredients should be stated on the label. For group (c), the analytical procedure should be based on characteristic constituents, if any.	R	R	R	R
17.3.5	Reference samples of herbal materials should be made available for use in comparative tests, e.g. visual and microscopic examination and chromatography.	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
17.3.6	Quantitative determination of known active components for members of groups (a) and (b) and of markers for members of group (c) is necessary.	R	R	R	R
17.3.7	The development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products should be in line with subsection 15.1 (Specifications). Tests and quality requirements that are characteristic of the given analyte should be selected.	R	R	R	R
17.3.8	Particularly for herbal materials in group d and for finished herbal products containing such materials, characteristic chromatograms (and/or fingerprint chromatograms) may be applicable. Using these methods may ensure that the main constituents can be easily followed throughout the production process. Caution is necessary, however, for every delivery of herbal materials and every batch of herbal preparations (including extracts) will have slightly different chromatograms/fingerprints resulting from differences in chemical compositions caused by intrinsic or extrinsic factors.	R	R	R	R
17.4	**Stability studies**				
17.4.1	If the expiry date for a herbal material or herbal preparation is given, some stability data to support the proposed shelf-life under the specified storage conditions should be available. Stability data are always required to support the shelf-life proposed for the finished herbal products.	R	R	R	R
17.4.2	Finished herbal products may contain several herbal materials or herbal preparations, and it is often not feasible to determine the stability of each active ingredient. Moreover, because the herbal material, in its entirety, is regarded as the active ingredient, a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Chromatography allows tracing of changes which may occur during storage of a complex mixture of biologically active substances contained in herbal materials. It should be shown, as far as possible, e.g. by comparisons of appropriate characteristic/fingerprint chromatograms, that the identified active ingredient (if any) and other substances present in the herbal material or finished herbal product are likewise stable and that their content as a proportion of the whole remains within the defined limits.	R	R	R	R
17.4.3	The fingerprint methods used for the stability studies should be as similar as possible to those used for quality control purposes.	R	R	R	R
17.4.4	For identified active ingredients, constituents with known therapeutic activity and markers, widely used general methods of assay, and physical and sensory or other appropriate tests may be applied.	R	R	R	R
17.4.5	To determine the shelf-life of finished herbal products, strong emphasis should also be placed on other tests in subsection 15.1 (Specifications), such as moisture content, microbial contamination and general dosage form control tests.	R	R	R	R
17.4.6	The stability of preservatives and stabilizers should be monitored. When these are not used, alternative tests should be done to ensure that the product is self-preserving over its shelf-life.	R	R	R	R
17.4.7	Samples used for stability studies should be stored in the containers intended for marketing.	R	R	R	R
17.4.8	Normally the first three commercial production batches should be included in the stability-monitoring programme to confirm the expiry date. However, where data from previous studies, including pilot batches, show that the product is expected to remain stable for at least two years, fewer than	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	three batches can be used. The testing frequency depends on the characteristics of the herbal medicinal products and should be determined on a case-by-case basis.				
17.4.9	The protocol for ongoing stability studies should be documented. This would normally involve one batch per year being included in a stability-monitoring programme.	R	R	R	R
17.5	**Packaging materials and labelling**				
17.5.1	All processed herbal medicines shall be packed in food grade containers that protect the product from any form of contamination or deterioration and labelled. All packaging materials, such as bottles and other materials, should be stored properly. Controls on the issue and use of these packaging materials should be adequate to ensure that incorrect labels and cartons are not used	R	R	R	R
17.5.2	All containers and closures should be thoroughly cleaned and dried before being used to pack the products.	R	R	R	R
17.5.3	There should be adequate information on the label (or the package insert) to inform the users of the composition of the product (in addition to the brand name, if any), indications or actions, directions for use, cautions and adverse reactions if any, and the expiry date.	R	R	R	R
17.5.4	Finished herbal products may contain several herbal materials and/ or herbal preparations. Unless otherwise fully justified, the full quantitative composition of the herbal ingredients should be stated on the product label. If this is not possible, at least the main ingredients should be stated on the label while the full qualitative composition could appear on the package insert.	R	R	R	R
17.5.5	The qualitative and quantitative particulars of the active ingredients in herbal materials and herbal preparations should be expressed in the following ways: — For herbal materials and herbal preparations consisting of comminuted or powdered herbal materials: (a) the quantity of the herbal material must be stated or, if constituents with known therapeutic activity are unidentified, the quantity of the herbal material/herbal preparation should be stated; or (b) the quantity of the herbal material/herbal preparation should be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see examples).	R	R	R	R
	— 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.	R	R	R	R
17.5.6	The composition of any solvent or solvent mixture used and the physical state of the extract should be identified.	R	R	R	R
17.5.7	If any other substance is added during the manufacture of the herbal preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) should be described as such or as “other ingredients” and the genuine extract as the “active	R	R	R	R

No.	Control criteria	Level of compliance			
		Bronze	Silver	Gold	Platinum
	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.				

Legend:

R = Required; G = General; O = Optional

Annex A
(informative)

Model certificate of good manufacturing practices

A model certificate of Good Manufacturing Practices (GMP) for a manufacturing site is suggested (see below). This is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce but is intended to serve in situations where a specific GMP certificate is requested by importers, exporters, procurement agencies and regulatory authorities. It is suggested that the certificate should remain valid for a period of 2 years from the date of issue, but not exceeding 3 years after the inspection was carried out.

It is recommended that, where possible, GMP certificates should have, e.g. security seals, watermarks or holograms, to help prevent counterfeiting, tampering and other fraudulent activities.

Letterhead of regulatory authority

Model Certificate of Good Manufacturing Practices

Certificate No: _____

On the basis of the inspection carried out on _____ [date] _____ we certify that the site indicated on this certificate complies with Good Manufacturing Practices for the dosage forms, categories and activities listed in Table A.1.

1. Name and address of site:

_____

_____

_____

2. Manufacturer's licence number:

_____

3. Table 1:

Dosage form(s)	Category(ies)	Activity(ies)

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured through this process lies with the manufacturer.

This certificate remains valid until _____ [date] _____ It becomes invalid if the activities and/or categories certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

Address of certifying authority:

_____

_____

Name and function of responsible person:

_____

_____

Email: _____ Telephone no.: _____ Fax no.: _____

Signature: Stamp and date:

_____

_____

Explanatory notes

(1) This certificate, which is in the format recommeded by WHO, certifies the status of the Site listed in point 1 of the certificate.

(2) The certification number should be traceable within the regulatory authority issuing the certificate.

(3) Where the regulatory authority issues a licence for the site this number should be specified. Record “not applicable” in case where there is no legal framework for the issuing of a licence.

(4) Table 1

List the dosage forms, starting materials, categories and activities. Examples give below.

Example 1

Pharmaceutical Product(s)	*Category(ies)*	*Activity(ies)*
Dosage form(s):		
Tablets	Cytotoxic	Packaging
	Hormone	Production, packaging, quality control
	Penicillin	Repackaging and labelling
Injectables	Cefalosporin	Aseptic preparation, packaging, labelling

Example 2

Pharmaceutical Product(s)	*Category(ies)*	*Activity(ies)*
Starting material(s):		
Paracetamol	Analgesic	Synthesis, purification, packing, labelling

Use, whenever available, International Nonproprietary Names (INNs) or otherwise national nonproprietary names.

(5) The certificate remains valid until the specified date. The certificate becomes invalid if the activities and/or categories certified are changed or if the site is no longer considered to be in compliance with GMP.

(6) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality Assurance of Pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection, Volume 2*, 1999. World Health Organization, Geneva and subsequent updates.

Annex B
(informative)

Guidance on good manufacturing practices: Inspection report

When a site at which pharmaceutical products are manufactured is inspected, the inspector(s) responsible must draw up a report containing the items listed below.

A. Manufacturer

(a) Name of inspected manufacturer.

(b) Address of inspected manufacturer (including telephone, fax, email and 24-hour telephone numbers).

(c) Address of manufacturing site if different from that given above.

(d) Site number (e.g. site master file or number allocated by the responsible authority).

(e) Manufacturing licence number, if applicable.

(f) Activities.

(g) Pharmaceutical products manufactured.

(h) Key personnel.

(i) Key persons met.

B. Inspection details

(a) Date(s) of inspection(s).

(b) Previous inspection date.

(c) Type of inspection.

(d) Scope of inspection.

(e) The regulatory authority.

(f) GMP guidelines used for assessing compliance.

(g) For foreign inspections state whether, the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection.

(h) Brief report of inspection activities undertaken.

(i) Samples taken and results obtained.

(j) Assessment of the site master file.

(k) GMP-related recalls from the market of any product in the last 2 years.

C. Inspector(s)

(a) Name(s) of inspector(s) and accompanying experts.

D. Introduction

(a) Brief summary of the manufacturing activities.

(b) Other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development).

(c) Use of outside scientific, analytical, or other technical assistance in manufacture and quality control.

(d) Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available.

E. Observations

The observations made during the inspection that are considered to be non-compliant with GMP should be listed. Where positive observations are included in the report, clear distinction should be made between "positive" and "non-compliant". Non-compliant observations can be classified, e.g. as "critical", "major" and "minor" if the Member State concerned has defined these terms. The date by which corrective action and completion are requested in accordance with the policy of the national regulatory authority should be given.

E.1 Quality assurance

(a) Quality system and documented quality policy of the manufacturer, e.g. as described in the quality manual.

E.2 Organization and personnel

(a) Organizational chart showing the arrangements for quality assurance, including production and quality control.

(b) Qualifications, experience and responsibilities of key personnel.

(c) Outline of arrangements for basic and in-service training and method of keeping records.

(d) Health requirements for personnel engaged in production.

(e) Personnel hygiene requirements, including clothing.

E.3 Premises

(a) Manufacturing areas (design, location etc.) used e.g. for storage and manufacturing (e.g. weighing, production, packaging) and flow of personnel and material.

(b) Special areas for the handling of highly toxic, hazardous and sensitizing materials.

(c) Nature of construction and finishes.

(d) Systems such as drainage, ventilation, air conditioning, and supply of steam and gas. Detailed description of critical areas with potential risks of contamination and cross-contamination.

(e) Classification of the rooms used for the manufacture of products, including clean rooms.

(f) Water systems.

(g) Planned preventative maintenance programme.

(h) Qualification of premises and systems as appropriate.

E.4 Equipment

(a) Design, location and adaptation of equipment used in production and control laboratories.

(b) Planned preventative maintenance programmes for equipment and records.

(c) Qualification and calibration, including records.

E.5 Materials

(a) Sourcing of materials.

(b) Control, storage and handling of materials, including:

— starting materials;

— packaging materials;

— intermediate and bulk products;

— finished products;

— returned and rejected materials;

— reagents and culture media;

— reference standards;

— waste material.

E.6 Good practices in production

(a) Transport, handling and use of starting materials, packaging materials, and bulk and finished products.

(b) Production operations and important parameters (e.g. sampling, quarantine, weighing, process operations and conditions, acceptance limits).

(c) Validation (e.g. process).

(d) Change control and deviation reporting.

E.7 Quality control

(a) Activities of quality control (including quarantine control, sampling, chemical and microbial analysis).

(b) Organization and personnel.

(c) Premises.

(d) Equipment and instrumentation.

(e) Materials.

(f) Documentation (e.g. specifications, procedures, reports, records).

E.8 Sanitation and hygiene

(a) Procedures for sanitation and/or cleaning (e.g. of premises and equipment) and records.

(b) Personal hygiene.

E.9 Validation

(a) Validation master plan.

(b) Validation and qualification protocols and reports for qualification and validation (e.g. of premises, systems, equipment, process, computer, cleaning, analytical methods).

(c) Stages of validation.

(d) Types of validation.

E.10 Documentation

(a) Documentation (e.g. specifications, procedures, records, protocols, reports).

(b) Preparation, revision and distribution of documentation.

(c) Reports on production, quality control (including environmental control), engineering and other relevant areas.

E.11 Complaints

(a) Procedure, records and investigation.

E.12 Product recalls

(a) Procedure, records and investigation.

E.13 Contract production and analysis

(a) Responsibilities of contract giver.

(b) Responsibilities of contract accepter.

(c) Contract (containing clearly defined responsibilities).

(d) GMP compliance of the contract accepter (initial assessment and continued compliance audited at regular intervals).

E.14 Self-inspection and quality audits

(a) Procedure, programme and compliance.

(b) Items for self-inspection.

(c) Self-inspection team.

(d) Frequency of self-inspection.

(e) Self-inspection report.

(f) Follow-up action.

(g) Quality audit.

(h) Suppliers' audits.

F. Summary

Brief summary of the findings, and recommendations (where applicable).

G. Conclusions

A statement regarding the GMP status.

Name: _____ Signature:_____ Date: _____

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