Annex 1

WHO guidelines on good herbal processing practices for herbal medicines

1. Introduction

1.1 Background to development of guidelines

1.1.1 Needs

Over the past three decades, there has been a constant, and at times, exponential growth in global interest in the use of herbal medicines. This increase in popularity and usage of herbal medicines is evident in the global market. Herbal medicines, including finished herbal products and the starting materials for their production, such as medicinal plants, herbal materials, herbal preparations and herbal dosage forms, are moving into international commerce and global trade, which reflects their increased economic value and importance.

Adverse events reported to the regulatory authorities in relation to the use of herbal products are often attributable to poor quality of source material and manufacturing and processing factors, among others. Correct identification of source plant species and the selection of appropriate parts for use in herbal medicines are basic and essential steps for ensuring safety, quality and efficacy of herbal medicines. Hence, the safety and quality of herbal medicines at every stage of the production process have become a major concern to health authorities, health care providers, the herbal industries and the public.

The safety and efficacy of herbal medicines largely depend on their quality. Unlike pharmaceutical products formulated from single-molecule chemicals produced synthetically or by isolation from natural source materials employing reproducible methods, herbal medicines consist of simple processed herbs or finished herbal products prepared from source materials containing a multiplicity of chemical constituents, the quality and quantity of which can vary from batch to batch due to intrinsic and extrinsic factors. Consequently, the quality of finished herbal products is greatly influenced by the quality of the raw materials and the intermediates; and the requirements and methods for quality control of finished herbal products, particularly for mixed herbal preparations, are far more complex than those employed for single-molecule chemical medicines.

A number of World Health Assembly (WHA) resolutions relating to traditional medicine have requested the World Health Organization (WHO) to provide technical support to develop methodology to monitor or ensure the safety, quality and efficacy of herbal medicines. The International Conferences of Drug Regulatory Authorities, and annual meetings of International Regulatory Cooperation for Herbal Medicines, as well as the Meetings of the National Centres Participating in the WHO International Drug Monitoring Programme have also requested WHO to develop and continuously update the technical guidelines on quality, safety and efficacy of herbal medicines.

1.1.2 Process and context

Participants of the WHO informal meeting on methodologies for quality control of finished herbal products (held in Ottawa, Canada in July 2001) looked at the overall picture of herbal medicines: from raw materials to the distribution and supply of finished herbal products, including key steps at which quality control is required.

One of the main recommendations of the meeting was that WHO should prepare a series of technical guidelines and documents covering quality control issues (from raw materials to finished herbal products), as well as to update existing documents.

Following the meeting's recommendations, and as a part of the implementation of relevant WHO strategies (notably, WHO traditional medicine strategies and WHO medicines strategies) and WHA resolutions, WHO undertook the development of four new guidelines and updated other existing documents. Their aim is to provide technical guidance on quality control required at key steps in the production of herbal medicines to support Member States in their efforts to ensure the quality of herbal medicines. These guidelines are:

- *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (*1*);
- *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues* (*2*);
- *WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines* (*3*); and
- *WHO guidelines on good herbal processing practices for herbal medicines* (present document).

WHO has also updated two key technical guidance documents:

- *WHO good manufacturing practices (GMP): supplementary guidelines for the manufacture of herbal medicines* (*4*), which was also reproduced in *WHO guidelines on good manufacturing practices (GMP) for herbal medicines* (*5*) and further updated (*6*); and
- *Quality control methods for herbal materials* (*7*), which includes the WHO good practices for pharmaceutical quality control laboratories as an annex.

1.1.3 Preparation of the guidelines

The original title suggested for these guidelines was "Good processing practices for herbal materials". The working draft guidelines were reviewed, and the objectives, scope and proposed contents were discussed and agreed to at the

second WHO consultation on quality control of herbal medicines (Hong Kong SAR, China in November 2014). The first draft guidelines were drafted and revised twice, through a global review process. The second revised draft was reviewed and discussed at the third WHO consultation on quality control of herbal medicines held in Hong Kong SAR, China, in September 2017. The draft was then further revised based on the discussion and consensus reached at the third WHO consultation.

1.2 Scope

Herbal processing encompasses the unique procedures of preparing herbal materials and herbal preparations, and it may be extended to the production of finished herbal products, with the ultimate goal of assuring herbal medicines quality. Thus, within the context of quality assurance and control of herbal medicines, the *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (*1*) cover the cultivation and collection of medicinal plants, together with certain post-harvest operations in which the concept of "post-harvest processing" is laid down. The good herbal processing practices (GHPP) set out in the present guidelines are intended to complement, and should be used in conjunction with, the GACP guidelines. On the other hand, the *WHO guidelines on good manufacturing practices (GMP) for herbal medicines* (*4–6*) have established general technical requirements for quality assurance and control in the manufacture of herbal medicines. In general, they cover the production steps following "post-harvest processing", including steps known as "processing". The GHPP guidelines are thus intended to supplement technical guidance on processing in the post-harvest stages.

In this scenario, GHPP is integrally linked to GACP and GMP, by elaborating on the post-harvest processing procedures (which are dealt by the former) and supplementing the latter on processing procedures for the production and manufacure of herbal medicines. These guidelines will provide technical guidance on GHPP in the:

- processing of herbs into herbal materials;
- processing of herbal materials into herbal preparations; and
- processing of herbal materials or herbal preparations into herbal dosage forms.

1.2.1 Processing of herbs into herbal materials

The concept of post-harvest processing set out in the GACP encompasses the immediate treatments accorded to herbs obtained from cultivation or field collection to free them from foreign matter, untargeted or extraneous plant

materials and other contaminants. Integral to the preparation of herbal materials are the procedures of "inspection" and "sorting", as well as "primary processing" procedures such as washing, disinfection, primary cutting, cooling, freezing and "drying". These processes are described in detail in these GHPP guidelines.

In addition, various other "primary processing" procedures are applied to herbs, as a single processing procedure or as combined procedures. These include a well-defined series of procedures intended to alter their toxicity or modify their medicinal activity. These procedures include advanced cutting and comminution (fragmentation), ageing, sweating (fermentation), baking/roasting, boiling/steaming, stir-frying and primary distillation. Technical information on these *primary processing* procedures, applied during the *post-harvest processing* process are also elaborated on in the present GHPP guidelines.

1.2.2 Processing of herbal materials into herbal preparations

The herbal materials described above may be used as herbal medicines. Such (processed) herbal materials intended for direct therapeutic use should be produced under GACP and GMP conditions. In many other cases, herbal materials will undergo further "processing" treatment procedures before being used to manufacture the finished herbal products. The active ingredients are usually processed together with other components of the herbal materials. Sometimes these active ingredients are further concentrated by the removal of inactive and/or undesirable substances. The herbal preparations thus obtained include extracts, decoctions, tinctures, essential oils and others. The processes involved include extraction, distillation, fractionation, concentration, fermentation, or other chemical or biological methods.

General guidelines for good practices in the production of herbal preparations and/or finished herbal dosage forms as set out in the GMP requirements prescribed by WHO guidelines (*4*–*6*, *8*) should be followed. Technical information on the key processes is supplemented in the present GHPP guidelines.

1.2.3 Processing of herbal materials or herbal preparations into herbal dosage forms

Depending on the intended use, herbal materials could be regarded as starting materials and herbal preparations could be regarded as intermediates in the process of producing finished herbal products, or as herbal dosage forms for therapeutic applications. In the latter case, simple herbal dosage forms may be prepared either from herbal materials (such as unprocessed seeds or plant exudates) or herbal preparations (such as ground powders and dried extracts) ready for administration to patients. These herbal dosage forms, produced under

GMP conditions, include decoctions, tea bags, granules, syrups, ointments or creams, inhalations, patches, capsules, tablets and pills, among others. Supplementary technical information on the key processes is included in these GHPP guidelines.

1.3 Objectives of the guidelines

These guidelines will provide technical guidance on GHPP for the production of herbal materials, herbal preparations and, ultimately, herbal dosage forms (guided by GMP). Under the overall context of quality assurance and control of herbal medicines, the main objectives of these guidelines are to:

- provide general and specific technical guidance on GHPP for herbal medicines;
- provide technical information on general as well as specific good herbal processing techniques and procedures applied to the preparation of herbal materials from herbs;
- provide technical information on good herbal processing techniques and procedures applied to the production of herbal preparations from herbal materials;
- provide supplemental technical information on good herbal processing techniques and procedures applied to the production of dosage forms of herbal medicines;
- provide a model for the formulation of national and/or regional good herbal processing practices guidelines and monographs for herbal materials, as well as for herbal preparations, and related standard operating procedures (SOP); and
- contribute to the quality assurance and control of herbal materials, herbal preparations and herbal dosage forms to promote safety, efficacy and sustainability of herbal medicines.

1.3.1 Use of these guidelines

These guidelines should be considered in conjunction with the existing WHO technical documents and publications relating to the quality assurance of herbal medicines and medicinal plants (for details, see references *1–16*).

The *WHO guidelines on good herbal processing practices for herbal medicines* is one of a series of guidance documents concerned with control measures necessary to produce quality herbal medicines for safe and efficacious use as directed by the regulatory authority concerned. The present document concerns the assurance of the quality of the herbal materials prepared by various

methods and processing steps from the herbs obtained under GACP. It also covers the herbal preparations prepared using various methods and processing steps from the herbal materials, as well the herbal dosage forms produced through various methods and processing steps from herbs, herbal materials or herbal preparations. Herbal materials and herbal preparations can be used directly as herbal medicines (when produced under GMP conditions), or can serve as source materials for the production of finished herbal products in accordance with GMP. These guidelines are applicable to the processing operations from post-harvest to herbal dosage forms. The processing of herbs, herbal materials and herbal preparations should meet all applicable national and/or regional quality standards. Adherence to local legislation, rules and practice in each Member State is mandatory. Each Member State should develop its own national guidelines on GHPP for herbal medicines that are appropriate to the country's situation.

1.4 Definitions of terms

The terms used in these guidelines are defined below. The terms and their definitions have been selected and adopted from other WHO documents and guidelines that are widely used by WHO Member States, as well as from other reference sources, publication details of which can be found in the reference list. These definitions may differ from those included in national regulations and are, therefore, for reference only.

It should be noted that as a consequence of the various types of "herbal medicines" produced, the same type of material may be classified in different ways (for example, powdered plant material may be both "herbal material" and "herbal preparation" or, in a packed form, "herbal dosage form" or "finished herbal product").

1.4.1 Terms relating to herbal medicines

Herbal medicines include herbs and/or **herbal materials** and/or **herbal preparations and/or finished herbal products** in a form suitable for administration to patients (*3*).

Note: In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (for example, animal and mineral materials, fungi, algae or lichens, among others).

Herbs (*16*)

Herbs include crude plant materials such as leaves, flowers, fruits, seed, stem wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials[1] (*16*)

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 plant materials.

Herbal preparations (*16*)

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

Finished herbal products (*3*)

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called "mixture herbal products").

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished 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".

Herbal dosage forms

Herbal dosage forms are the physical form (liquid, solid, semi-solid) of herbal products produced from herbs, with or without excipients, in a particular formulation (such as decoctions, tablets and ointments). They are produced either from herbal materials (such as dried roots or fresh juices) or herbal preparations (such as extracts).

Medicinal plants are plants (wild or cultivated) used for medicinal purposes (*1*, *4*–*6*).

Medicinal plant materials: see Herbal materials

[1] The participants of the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that latex and exudates can be included.

1.4.2 Terms relating to herbal processing practices

Herbal processing

Herbal processing refers to the overall treatment in the course of production of herbal materials, herbal preparations and herbal dosage forms. For the purpose of the present guidelines, herbal processing includes "post-harvest processing" described in the *WHO guidelines on GACP for medicinal plants* (*1*), as well as "processing" procedures and protocols set out in the *WHO guidelines on GMP for herbal medicines* (*4–6*, *8*).

Post-harvest processing

Post-harvest processing covers any treatment procedures performed on the herbs after harvest or collection when they are being processed into herbal materials. It includes processes such as inspection, sorting and various primary processing and drying. Often, well-defined combined or serial procedures are applied to herbs before they can be used in therapeutic treatment or as intermediates for manufacturing finished herbal products. These treatment processes are considered important pharmaceutical techniques in the herbal industry, through which purity and/or quality of raw herbs is assured (such as prevention of microbial and insect infection or infestation), and the therapeutic properties of raw herbs are altered (such as enhancement of effectiveness or reduction of toxicity). These primary processing procedures may vary from one herbal material to another, depending on its chemical and pharmacological characteristics, as well as the intended therapeutic purposes.

Adjuvants

Adjuvants are adjunctive substances added during the herbal processing procedures for the purpose of altering the pharmacological or therapeutic properties of the herbal materials, neutralizing or reducing toxicity, or masking the taste, assisting formulation into suitable herbal dosage forms, maintaining stability or extending the storage time. Common adjuvants include water, wine, vinegar, honey, milk and clarified butter, among other materials.

1.4.3 Terms relating to quality control

A comprehensive list of terms relating to the quality control of herbal medicines can be found in the *WHO guidelines on GMP for herbal medicines* (*5*, *6*), *Good manufacturing practices for pharmaceutical products: main principles* (*8*), *Quality control methods for herbal materials* (*7*), and *WHO guidelines for selecting substances of herbal origin for quality control of herbal medicines* (*3*). The following terms are more applicable to the present guidelines.

active ingredients refer to constituents with known therapeutic activity, when they have been identified. When it is not possible to identify the

active ingredients, the whole herbal medicine may be considered as an active ingredient (*3*).

batch (or lot)[2] (*5*, *8*, *17*). A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number) (*5*, *8*, *17*). A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

chemical reference substance (or standard) (*17*). An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

constituents (*3*). Chemically defined substances or group/group(s) of substances found in a herbal material or herbal preparation.

contamination[3] (*5*, *8*, *17*). The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

cross-contamination (*5*, *8*, *17*). Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

good manufacturing practice (GMP) (*8*). GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and quality control. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

in-process control (*5*, *8*, *17*). Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product

[2] The participants at the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that in case of terminal sterilization, the batch size should be determined by the capacity of the autoclave or any other sterilization equipment.

[3] The participants at the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017 recommended that the term "physical" should be added before the term "chemical".

conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

markers (marker substances) (*3*). Reference substances that are chemically defined constituents of a herbal material. They may or may not contribute to their therapeutic activity. However, even when they contribute to the therapeutic activity, evidence that they are solely responsible for the clinical efficacy may not be available.

master formula (*5*, *8*, *17*). A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

specification (*5*, *8*, *17*). A list of defined requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (*5*, *8*, *17*). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (for example, equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

2. Good herbal processing practices for the production of herbal materials

2.1 General information

Post-harvest processing is often specific to the herb and may involve unique procedures. The particular processing method may be a practice based on a tradition as old as the use of medicinal plants, and/or it may be based on proprietary procedures. In either case, herbal processing procedures should be subjected to good practice standards.

Herbs obtained from field collection or cultivation should be subjected to a series of good practice post-harvest processing procedures set out in the GACP guidelines (*1*). In general, post-harvest processing of herbs includes inspection and sorting, primary processing and drying. The exact herbal processing procedures may vary from one herb to another. Thus, some procedures consist of only a few simple steps of primary processing such as cleaning, primary cutting and sectioning, before being dried. Others may require more complicated steps such as advanced cutting and sectioning (for example, decoction pieces processing), comminuting, ageing, sweating (fermentation), baking/roasting, boiling/steaming and stir-frying, for the purpose of improving

the quality, preventing damage from mould and other microorganisms, detoxifying intrinsic toxic ingredients or enhancing therapeutic efficacy. The present GHPP guidelines elaborate and supplement the GACP guidance.

In all cases, good in-process control measures should be employed to assure the quality of the end-product. National and/or regional botanical and chemical quality standards for each processed herbal material should be met. In the absence of national standards, regional or international pharmacopoeial standards may be adopted. Guidance on compliance measures can be found in the annex to the *Quality control methods for herbal materials* (*7*), *WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines* (*3*), *WHO guidelines on GACP for medicinal plants* (*1*), WHO guidelines on GMP for herbal medicines (*4–6*, *8*), and the present guidelines.

2.2 Purposes and functions of primary processing

Simple post-harvest processing (such as sorting, washing and leaching) serves to remove dirt and other unwanted materials from the herbs after they have been harvested or collected from the growing site. Unless intended for use in its fresh form, the herb is subjected to a drying procedure, immediately or shortly after harvesting, in order to minimize damage from mould and other microbial infestation.

Through experience gained over the centuries, knowledge has been acquired for the development of various primary processing procedures for maximizing the quality and therapeutic value of herbal medicines. The final form of a herbal material depends upon the nature of the herb and its intended use. In general, primary processing of herbs serves several purposes, such as concentrating the ingredients; removing undesirable substances; modifying the therapeutic properties; reducing toxicity; facilitating dispensing, compounding and storage. The major objectives of primary processing of herbal materials are summarized below.

2.2.1 Neutralization of toxicity and diminishing side-effects

Herbal materials that possess significant toxicity, highly potent pharmacological activity or are known to cause severe side-effects, should be pretreated in specific manners in order to neutralize the toxicity or to reduce the side-effects prior to use. Such a detoxifying process is particularly important for those herbs that are known to contain toxic or undesirable chemical components; they must be properly processed to remove those unwanted substances. Through the primary processing processes such as steaming and frying, heat-sensitive toxic components will be degraded. In other cases, processes such as sweating (for example, fermentation) and ageing result in enzymatic degradation of the toxic ingredients. For example, raw aconite (*Aconitum carmichaelii* Debeaux or

related species) root, containing significant amounts of toxic alkaloids such as aconitine, must be boiled or steamed for hours to hydrolyse aconitine into less toxic derivatives. In the case of cascara (*Frangula purshiana* Cooper), the bark that has been collected or harvested should be kept (aged) for at least one year before use. This is to allow oxidation to occur, by which the strongly purgative hydroxyanthracene glycosides are converted to oxidized compounds with lower laxative potencies.

2.2.2 Modification of therapeutic properties

Some herbal materials require primary processing to alter their therapeutic properties. For example, rhubarb (rhizome of *Rheum* spp.) in its raw form possesses purgative action and is useful as a cathartic. After being steamed with wine, however, the purgative action is attenuated and the processed rhubarb can be used for other purposes such as reducing inflammation.

The specific medicinal property of some herbal materials may be changed through primary processing. For example, the unprocessed raw rehmannia (*Rehmannia glutinosa* (Gaertn.) DC.) root is used to treat fever, hypertension and skin eruptions. After being cooked in wine, however, the processed rehmannia is often used for tonic and anti-ageing purposes in some traditional medicine contexts.

In the case of ginseng (*Panax ginseng* C.A. Mey.) roots, different primary processing procedures give rise to several processed products, such as white ginseng and red ginseng. White ginseng is the herbal material dried in the sun or by heat, whereas red ginseng is prepared through a series of steaming and cooking steps. These two types of ginseng products have different therapeutic uses in some traditional medicine contexts, red ginseng being more potent than white ginseng in its warming or energizing effects.

2.2.3 Enhancing efficacy and reinforcing therapeutic effects

The therapeutic efficacy of certain herbal materials can be augmented through primary processing in some traditional medicine contexts. For instance, the pain-relieving property of corydalis (*Corydalis yanhusuo* W.T. Wang) rhizomes is believed to increase when they are stir-fried with rice vinegar.

2.3 Post-harvest processing procedures

Raw herbs should be inspected and sorted immediately following harvest or collection. They are then subjected to a series of on-site primary processes, and in most cases, subjected to further processes at a processing facility. The exact processing methods may differ from one herb to another, and the guidelines therefore may need to be adjusted on a case-by-case basis.

An example of a model format for a GHPP monograph/SOP protocol is given in Appendix 1.

2.3.1 Sorting (garbling)

The sorting process serves as the first step to ensuring the purity and cleanliness of the herbs. After the bulk amount of the desired plant part has been harvested or collected, all extraneous and unwanted matter including dirt (for example, soil, dust, mud and stones), impurities (for example, insects, rotten tissues, untargeted/extraneous medicinal plant(s) and/or plant part(s)), and residual non-medicinal as well as toxic part(s) must be removed from the medicinal part(s). Depending on the herb, the process may involve procedures such as:

- removing dirt and foreign substances;
- discarding damaged parts;
- peeling (to separate unwanted plant part(s) from the medicinal plant part(s) such as removing unwanted root bark from the roots or collecting stem bark from the stem);
- sieving, trimming, singeing (to remove hairs or rootlets);
- removal of residues of unwanted plant part(s) (for example, removing unwanted seeds from fruits and stripping leaves from stems).

Although in some cases sorting may be done by mechanical means, it is usually done by hand. Only staff who are suitably trained and equipped (for example, wearing gloves and a dust mask, etc. as appropriate) should carry out this work.

2.3.2 Primary processing

Washing

Raw herbs, especially roots, rhizomes and tubers, are usually washed with clean water and dried soon after harvest or collection. During the washing process, scraping and brushing may be necessary. It is generally recommended not to soak the herbs in water for an unnecessarily long period. Water should be changed as frequently as required. The use of water containing a low concentration of chlorine (for example, sodium hypochloride, bleach) to prevent microbial fermentation is recommended where and when possible or practical.

Leaching

Some impurities can be removed by the action of running water over the raw herbs (leaching). The duration of leaching has to be controlled in order to prevent excessive loss of active ingredients.

Primary cutting

Bulky raw herbs that have been harvested or collected may require primary cutting to reduce their size before transportation to the processing or manufacturing facility. Primary cutting is usually performed at or near the harvest or collection site.

Ageing

The ageing process refers to storing the herbal materials for a period of time after harvesting or collection from the field prior to use. Herbs are generally aged in the sun or in the shade, depending on the specific herbal material. During the process of ageing, excessive water is evaporated and enzymatic reactions (such as hydrolysis of the glycone portion of glycosides) or oxidation may occur to alter the chemical composition of the herbal material. For example, in cascara (*Frangula purshiana* Cooper) bark, after proper ageing (at least one year, or having been artificially heated to speed up the process), the reduced forms of the emodin glycosides in the fresh bark are converted to monomeric oxidized emodin glycosides. The latter form of glycosides are milder cathartic agents, with reduced irritating effects that may cause vomiting and stomach upsets, and hence, are more suitable as a therapeutic agent.

Sweating

A similar process known as sweating (for example, fermentation) involves keeping the herbal materials at a temperature of 45–65 °C in conditions of high humidity for an extended period, from one week to two months, depending on the plant species. The sweating process is considered a hydrolytic and oxidative process in which some of the chemical ingredients within the herbal materials are hydrolysed and/or oxidized.

The herbal materials are usually densely stacked between woollen blankets or other kinds of cloth. For example, vanilla beans (*Vanilla planifolia* Jacks. ex Andrews) are well known to undergo repeated sweating between woollen blankets in the sun during the day and packed in wool-covered boxes at night for about two months. During this process, the vanilla pods lose up to 80% of their weight and take on the characteristic colour and odour of vanilla.

Parboiling (blanching)

After washing, certain herbal materials may undergo a parboiling or blanching process in which they are put into boiling water for a brief period without being fully cooked. Such a heating procedure may serve several purposes, such as improving storage life of the processed materials by gelatinizing the starch, preventing mould or insect contamination, easily drying, destroying enzyme

activity to prevent the alteration of certain chemical constituents, and facilitating further processing such as removal of the seed coat of almonds.

Boiling or steaming

The boiling process involves cooking the herbal materials in water or another liquid such as vinegar, wine, milk or other vehicle.

In the steaming process, herbal materials are kept separate from the boiling water but have direct contact with the steam, resulting in a moist texture of the herbal materials. Often, the herbal materials are placed in a steamer or in a special utensil equipped with a flat frame suspended over boiling water. In some cases, the herbal materials are pre-mixed with excipient substances such as wine, brine or vinegar before being steamed. The boiling or steaming process serves to soften plant tissues, to denature enzymes present in the herbal materials, and/or to thermally degrade selected chemical constituents. At the same time, the excipient, if used, is absorbed into the plant tissues to become an integral part of the processed herbal materials. For example, *Reynoutria multiflora* (Thunb.) Moldenke (synonym *Polygonum multiflorum* Thunb.) root is often steamed in the presence of a black bean (*Phaseolus vulgaris* L.) decoction in order to enhance its tonic effects. Boiling the raw herbs such as *Croton tiglium*, *Abrus precatorius*, *Nerium oleander* and *Gloriosa superba* L., in cow's milk is practised in some traditional medicine contexts to reduce the levels of their toxic ingredients and thus diminish the toxicity of the herbal materials.

Baking or roasting

The baking or roasting process is a dry-heating using indirect, diffused heat, where the herbal materials are put in a heating device. The herbal materials are often embedded in bran or magnesium silicate (talc) powder to ensure even heating over the entire surface at an elevated temperature for a specified period of time. Some herbal materials are wrapped in moistened papers during the roasting process. The exact temperature used and duration of baking or roasting vary from one herbal material to another. Some are baked or roasted until the surface colour turns yellowish brown; some may be further heated until charred. For example, nutmeg (*Myristica fragrans* Houtt.) and kudzu (*Pueraria montana* var. *lobata* (Willd.) Sanjappa & Pradeep) root require roasting before they are used for medicinal purposes.

Stir-frying

Stir-frying is a process in which the herbal materials are put in a pot or frying pan, continuously stirred or tossed for a period of time under heating until the external colour changes, charred or even carbonized. Depending

on the plant species, the stir-frying process may require the addition of adjuvants such as wine, vinegar, honey, saline and ginger juice, which would be infused into the herbal matrix to become an integral part of the processed herbal material.

To ensure even heating over the surface of the herbal materials, sand, rice, bran, talc or clay can be admixed with the herbal material during stir-frying.

For example, liquorice (*Glycyrrhiza* glabra L. and *G. uralensis* Fisch.) root and rhizome and Astragalus roots (*Astragalus mongholicus* Bunge or *A. membranaceus* (Fisch.) Bunge) are often stir-fried with honey for the preparation of decoction slices, whereas the *Salvia miltiorrhiza* Bunge root is stir-fried with wine. Fresh ginger is often stir-fried with sand until the surface colour turns brown. In other instances, ginger can be further stir-fried over intense fire to a carbonized state for use as decoction pieces.

Fumigation

Fumigation with sulfur dioxide has been employed in post-harvest handling of some herbs for the purpose of preserving colour, improving fresh-looking appearance, bleaching, preventing the growth of insects and inhibiting decay caused by moulds. Thus, the process has been frequently applied to herbal materials of light and bright colours to avoid "browning". Due to concerns about the undesirable residues, this process should be avoided as far as possible. When a real need is identified, treatment should be carried out at the earliest possible stage and exclusively by adequately trained and qualified personnel, according to the specific recommendations for use. All relevant regulations (for example, limits on sulfite residue) should be complied with.

Irradiation

In some cases, irradiation or ultraviolet light can be used to eliminate or reduce microbial load of the herbal materials. The use of these procedures has to comply with the national and/or regional regulations.

Advanced cutting, sectioning and comminution

When thoroughly dried, the herbal materials are processed by cutting and sectioning into convenient or specific sizes and shapes or forms for storage, direct use as decoction slices or pieces, and/or for further processing for the manufacture of herbal preparations or herbal dosage forms. Decoction slices or pieces are available in many Member States for direct use as herbal medicines. Where applicable, the entire, sectioned or cut herbal materials are comminuted or pulverized into powder form in accordance with common herbal medicines practice, for use as herbal dosage forms.

White and/or red ginseng products presented as root pieces, slices or in powder form prepared from appropriately dried roots of *Panax ginseng* C.A. Mey., marketed as herbal medicines, are good examples of herbal materials derived from simple processing procedures.

Other primary processing procedures

Other primary processing procedures may be applied to raw herbs at an early stage for the production of herbal materials, such as collection of gums or resins. Also included under the term primary processing are primary distillation of raw herbs to obtain crude essential oils and expression to obtain fresh juice. Such procedures are usually performed in the processing facility under GMP conditions.

2.3.3 Drying

Unless used in the fresh state, the raw herbal materials need to be dried after being sorted and washed. In general, they must be dried as soon as possible to protect them from mould and other microbial infestation. Drying will also prevent tissue deterioration and phytochemical alteration caused by the actions of enzymes and microbial organisms. It will also facilitate grinding and milling, and converts the herbal materials into a convenient form for further processing. However, attention must be given to the potential loss of volatile (for example, essential oil) constituents present in the fresh material.

The final moisture content for dried herbal materials varies depending on the tissue structure, but should ideally be below 12%. Information on the appropriate moisture content for a particular herbal material may be available from pharmacopoeias or other monographs.

Proper drying involves four major aspects: control of temperature, humidity, airflow and cleanliness of the air. The drying conditions are determined by the nature of the raw medicinal plant material to be dried (tissue structure and chemical composition) and by the desired appearance of the final form. The drying method used may have considerable impact on the quality of the resulting herbal materials. Hence, the choice of a suitable procedure is crucial. Information on appropriate drying methods and procedures for particular herbal materials may be available from pharmacopoeias or other authoritative monographs. Raw herbal materials are most often dried by sun-drying, shade-drying or by artificial heat.

The drying conditions chosen should be appropriate to the type of the herbal material. They are dependent on the characteristics (for example, volatility and stability) of the active ingredients and the texture of the plant part collected (for example, root, leaf or flower). Generally, one of the following drying processes can be adopted.

Sun-drying

Some herbal materials can be dried in the open air under direct sunlight, provided the climate is suitable. The duration of the drying process depends largely on the physical state of the herbal material and the weather conditions.

For natural drying in the open air, medicinal plant materials should be spread out in thin layers on drying frames and kept away from sources of possible contamination such as vehicle exhaust, heavy dust and rain. They should also be protected from insects, rodents, birds and other pests, livestock and domestic animals. The material should be turned periodically to achieve uniform drying. The drying frames should generally be set up at a sufficient height (for example, 15 cm) above the ground. Efforts should be made to achieve uniform drying within the shortest possible time to avoid mould formation.

Shade-drying

Herbal materials can be dried in the shade with or without artificial airflow to avoid direct exposure to strong sunlight. The drying process is slow, but it is preferred when it is necessary to maintain (or minimize loss of) colour of leaves and flowers. Low temperatures (relative to heat-drying) will also preserve most of the volatile and aromatic components by reducing evaporation.

Drying by artificial heat

Drying by artificial heat can be faster than open-air drying and is often necessary on rainy days or in regions where the humidity is high. Drying of herbal materials may be done using ovens, stoves, rack dryers, solar dryers, tunnel dryers, belt dryers, other heating devices or open fires. The use of an open fire should be avoided as much as possible, as residues of combustion may introduce contamination. When an open fire is used, the area must be well ventilated.

For artificial heat-drying, the temperature, humidity and other conditions should be governed by the physical nature of the herbal material being dried and the physical/chemical properties of its active ingredients. Over-heating may lead to an excessive loss of the volatile components and/or decomposition of chemical constituents. In general, the temperature should be kept below 60 °C for bark and root and below 40 °C for leaves, herbs and flowers.

2.4 General issues

2.4.1 Selection of processing method

Herbal materials derived from the same species but processed by different methods may show significant differences in quality and therapeutic properties, owing to the influence of the treatment process on the chemical composition.

It is not uncommon to find different processing methods being used for the same herb or herbal material, depending on intended use. For example, raw (unprocessed) liquorice is used as an antitussive and expectorant; but after being stir-fried with honey or ghee, the processed liquorice becomes a tonic drug to be used for replenishing body strength.

Prior to processing, it is important to consult the national or regional regulatory standards and other literature sources to decide on the most appropriate method to use. Once a method has been adopted, adherence to the SOP is necessary to ensure batch-to-batch consistency. For industrial production, method validation should be adopted as part of the SOP.

Only suitably trained staff should carry out the work, which should be conducted in accordance with the SOP and national and/or regional regulations in the countries where the plants are grown/collected and manufactured and in which the end-users are located.

2.4.2 Temperature

With in-processing procedures that involve heating, the temperature used is critical. It is necessary to ensure that the required temperature is achieved during the process. In some cases, preheating the equipment (for example, oven, frying pan and steamer) and/or the additives (such as sand, bran and rice) is required before putting in the herbal materials. When heating equipment is used, it should be regularly calibrated.

2.4.3 Duration of procedure/treatment

It is also critical to control the duration of the procedure or treatment of the herbal materials. Both over- and under-treatment will affect the quality of the resulting materials. Duration of the procedure or treatment should be monitored through adequate in-process controls performed on the basis of organoleptic alterations (such as changes in colour, odour, taste and texture) or changes in the contents of active chemical constituents with appropriate instruments or testing.

2.4.4 Use of adjuvants

Common adjuvants used during the processing procedures include water, wine (for example, rice wine, wheat wine and sorghum wine), vinegar, honey, ginger juice, liquorice extract, ghee, brine and so on. Under special circumstances, other adjuvants such as cow's milk, goat's milk, animal bile, goat fat, cow's urine, butter, black bean extract, coconut water, tamarind juice, turmeric, lemon juice and mineral materials (for example, borax) have been used.

The quality of adjuvants must be clearly defined and controlled (according to pharmacopoeial and/or relevant regulatory requirements). The exact amounts and quality of these adjuvants used (the ratio of herbal material and the adjuvant) should also be consistent from batch to batch. In addition, the use of any materials derived from animals or animal products in any processing procedures should be evaluated for safety and contamination, especially with pathogens, prior to use. General guidance is available in *Safety issues in the preparation of homeopathic medicines* (*9*).

2.5 Documentation

All processing procedures that could affect quality and safety of herbal materials should be documented. Guidance for good documentation can be found in *Good manufacturing practices for pharmaceutical products: main principles* (*5*, *8*, *17*), as well as *WHO guidelines on good agricultural and collection practices for medicinal plants* (*1*). Thus, it is important to establish a record-keeping system so that all records are up to date, maintained and traceable for the entire processing procedures for each batch of herbal materials.

Written processing records should include, but not be limited to, the following information:

- name of herbal material – botanical name (binomial – genus, species, with the authority (abbreviations, if used, should follow internationally accepted rules)) and the plant family name of the medicinal plant are essential. If required by national legislation, synonyms and applicable subspecies, variety, cultivar, ecotype or chemotype should be documented; if available, the local and English common names should also be recorded;
- plant part(s) of the medicinal plant or herb;
- stage of vegetative development, for example, flowering and fruiting, vegetative maturation;
- site/geographical location (if possible, based on GPS data,) and time of harvesting/collection;
- state of the medicinal plant or herb (for example, fresh or dried);
- batch number, batch size and any other identification code;
- name of supplier;
- dates of receipt of the material, processing of the material, and completion of the process;
- name of person in charge of the processing, and person in charge of batch release;

- general processes that the plant material has already undergone (for example, drying, washing and cutting, including drying time and temperatures, and size of herbal material);
- gross weight of the plant material before and after processing;
- method used for special processing;
- details of the procedures (master formula), including descriptions of the utensil and equipment used, steps of operation, manufacturer, specification, amount and quality grade of the adjuvant (for example, wine or vinegar) and/or other substances (for example, sand, bran) used, temperature control, length of processing time, after-process steps (for example, cooling, drying, cutting), and other relevant information;
- details of animal-derived materials or adjuvants used and their microbiological certificates, if applicable;
- batch production – detail deviations from or modifications of the master formula;
- in-process control, for example, organoleptic changes of the herbal material before and after processing (such as change in colour, shape, texture, odour and taste);
- quality control parameters, grades and/or specifications, and assay results, where appropriate, of active ingredient(s), markers or chemical reference standard(s);
- storage conditions and containers; and
- shelf life/retest period.

3. Good herbal processing practices for the production of herbal preparations

3.1 General information

The herbal materials described in section 2 of these guidelines may be ready to serve as the starting materials for use as herbal medicines. In some cases, they are cut into sections or ground into powder and used directly as the final dosage form. But often the herbal materials will undergo further treatment processes before being used to manufacture the finished herbal products. The ingredients are usually not purified and the extracts are further concentrated by the removal of inactive and/or undesirable substances.

Herbal preparations are thus obtained by subjecting the herbal materials to treatments such as extraction, distillation, fractionation, concentration,

fermentation, or other physicochemical or biological methods. The resulting preparations include extracts, decoctions, tinctures, essential oils and others.

3.1.1 Preparation of herbal materials for processing

- The quality of herbal materials should meet the requirements specified in the national pharmacopoeia or recommended by other documents of the end-user's country.
- Authentication of herbal materials should be performed prior to extraction. Purity (absence of contaminants) should also be ensured.
- Proper documentation on the herbal material should be available as recommended in section 2.5.
- The herbal material should be cleaned, dried (unless fresh material is required), and comminuted into an optimal size for extraction.
- The herbal materials should be processed as soon as possible after arrival at the processing facility. Otherwise they must be properly stored to avoid contamination, damage and deterioration (for example, loss of active constituents).
- All operational steps should be reproducible and performed hygienically, in accordance with the processing SOP.

In general, for processes such as extraction, fractionation, purification and fermentation, the rationale for the guidelines should be established on a case-by-case basis. An example of a model format for a good herbal processing practice monograph/SOP protocol to produce a herbal preparation is given as Appendix 2. General guidance is provided below.

3.2 Extraction

Extraction is a process in which soluble plant chemical constituents (including those which have therapeutic activity) are separated from insoluble plant metabolites and cellular matrix, by the use of selective solvent (which is sometimes called the menstruum). The purpose of extraction of herbal material is to eliminate unwanted materials and to concentrate other chemical constituents in a soluble form. Herbal extracts include liquid (fluid) extracts, soft extracts, oleoresins, dry extracts and others. The herbal preparations so obtained may be ready for use as medicinal agents, or they may be further processed into herbal dosage forms such as tablets and capsules.

Various techniques are used for extraction, including maceration, infusion, digestion, percolation – including hot continuous (Soxhlet) extraction – and decoction. Other extraction techniques can also be applied, for example,

heat reflux extraction, counter-current extraction, microwave-assisted extraction, ultrasonic extraction (sonication) and supercritical fluid extraction.

3.2.1 Common methods of extraction

In order to produce herbal preparations of defined quality, the use of appropriate extraction technology, extraction conditions, extraction solvents, ratio between herbal material and solvents, and type of equipment are crucial. Some common methods of extraction are described below.

Maceration

Maceration involves the procedures of mixing the properly comminuted herbal materials with the solvent and allowing the mixture to stand at a certain temperature for a defined period of time, agitating as necessary. During the maceration process, chemical constituents are extracted from the plant tissues through a dissolution process into the liquid solvent. Often the herbal material is put in a container and solvent added until the herbal powder is thoroughly moistened. An additional quantity of solvent is then introduced. The mixture is agitated at regular intervals for a defined period of time, strained, and the marc (the solid material) is pressed, to collect residual extract. All liquids are collected, combined and separated by decantation, centrifugation, straining or filtration. The maceration process may be repeated with fresh solvent if desired. In the process of maceration, the herbal materials are macerated in definite quantities of a solvent (at an optimal ratio of the amounts of herbal material to solvent), for a specified duration of time. Exhaustive bulk extractions via maceration can be quite time-consuming and require large volumes of solvent.

In specific cases, a modified maceration procedure involves pre-soaking the herbal material in water for a period of time to induce fermentation. In other cases, maceration can be performed by gentle heating in order to enhance the extraction efficiency in a process known as "digestion".

"Sonication-assisted extraction" and "microwave-assisted extraction" are modified methods of maceration, in which ultrasound or microwaves are utilized to enhance the extraction efficiency, to reduce the amount of solvent used, and to shorten the extraction time.

For *sonication*, the herbal material is placed in a container together with a solvent, which is in turn put in an ultrasonic bath. The ultrasound provides sufficient power to break down the cell walls of the herbal material and facilitates the solubilization of metabolites into the solvent. The frequency of ultrasound, length of treatment and temperature of sonication are important factors affecting the extraction yield.

For *microwave-assisted extraction*, the herbal material is placed in a container together with water, or another suitable solvent and subjected to

microwave treatment. Heat generated by the microwave energy facilitates the dissolution of compounds from the herbal matrix into the solvent.

Sonication-assisted and microwave-assisted extraction are rarely applied to large-scale extraction; they are used mostly for the initial extraction of a small amount of material.

Infusion

Infusion refers to an extraction procedure in which boiling water is poured on the herb or herbal material to produce a dilute liquid preparation. Typically, the herb or herbal material is allowed to stand for some time (usually 5–20 minutes). Sometimes another quantity of hot water is added and allowed to stand for additional time. The extracted plant material is removed by straining and the infusion is ready for use. Infusion is commonly employed to make herbal teas.

Percolation

Percolation is the procedure in which the solvent is allowed to continuously flow through the herbal material in a percolator (a vessel with an outflow at the bottom end). Typically, the properly comminuted herbal material is moistened with an appropriate amount of solvent and allowed to stand (macerate) for a few hours before being packed into the percolator. Additional solvent is added to totally wet the comminuted herbal material for some time. The bottom end (valve) of the percolator is then opened (adjusted), with fresh solvent being replenished from the top of the percolator to maintain a steady flow of solvent through the bed of herbal material. The flow rate of the liquid is controlled by adjusting the valve of the outlet. The extraction liquid is collected from the bottom outlet of the percolator. When the process is completed, the marc may be pressed and all liquids pooled to obtain the percolate. In addition to the solvent used for the extraction, the flow rate and the temperature influence the extraction yields and they have to be carefully controlled. Percolation is often used for an exhaustive extraction of the herbs and is applicable to both initial and large-scale extraction. In some cases, the process of percolation can be modified by applying vacuum to increase the flow of solvent.

A special technique of percolation is the "continuous (Soxhlet) extraction" process using the Soxhlet or Soxhlet-like apparatus. Usually, 50–60 cycles are necessary for complete extraction. Due to the continuous extraction, this method is more efficient than simple percolation and consumes less solvent. However, due to continuous heating at the boiling-point of the solvent used, thermolabile compounds may be damaged and/or artefacts may be formed. Besides the laboratory-scale setup for continuous extraction, industrial-scale stainless steel extractors and high-pressure extraction are commonly used in many manufacturing facilities.

Decoction

Decoction is the most common method for making herbal preparations in various traditional medicine contexts. It involves boiling the herbal material in water, during which time the chemical constituents are dissolved or extracted into the hot liquid. This procedure is suitable for extracting soluble and heat-stable active constituents of the herb or herbal material.

Supercritical fluid extraction

Supercritical fluid extraction is a modern technique making use of the solvating property of a fluid in its supercritical state (carbon dioxide is the most common supercritical solvent) to dissolve the chemical constituents in herbal materials. The density of the supercritical fluid (thus its solvating property) can be adjusted by altering the temperature and pressure, or by the addition of modifiers (for example, ethanol) to change the polarity of the supercritical fluid.

3.2.2 Steps involved in the extraction of herbs and herbal materials

The following steps are generally involved in the extraction procedures.

Comminution, fragmentation, grinding or milling **(see also section 2.3.2)**

Prior to extraction, the herb is generally dried and reduced to a size of 30–40 mesh sieves (the actual size can be adjusted if necessary). If fresh material is used for extraction, it is necessary to perform extraction as soon as possible after collection to avoid deterioration (microbial fermentation). The purpose of powdering the herbal material is to rupture its tissues and cell structures so that the chemical ingredients are more readily exposed to the extraction solvent. Moreover, size reduction increases the surface area, which in turn enhances the mass transfer of chemical ingredients from plant tissue to the solvent. However, excessive grinding can degrade the herbal material through mechanical heating and oxidation from exposure to air. Further, an excessively fine powder may block the pores of the extraction filter, slowing down or preventing the passage of the filtrate; it may even coalesce in the presence of the extraction solvent to form solid lumps, cakes or bricks, not amenable to being extracted.

Extraction

The extraction process is carried out in the selected solvent at a desirable temperature for an optimal period of time. Depending on the polarity of the desired chemical constituents, water or other solvents can be used, either at room temperature ("cold" extraction) or at an elevated temperature ("hot" extraction).

Sequential extraction with a series of solvents of differing polarity is sometimes done to create a series of extract fractions. In this procedure, the

herbal material is subjected to organic and aqueous solvents in a sequence of increasing polarities, for example, n-hexane, dichloromethane, ethyl acetate, water-saturated n-butanol and water. As a result, chemical constituents possessing different polarities are transferred from the herbal material to different solvent fractions according to the principle of "like dissolves like". For example, the initial step of extraction using non-polar solvents (such as n-hexane or petroleum ethers) removes lipophilic constituents (such as alkanes, fatty acids and sterols) from the herbal material in a process sometimes referred to as "defatting". The compounds with intermediate polarity (such as flavonoid and quinone aglycones) will dissolve in the medium-polarity solvents (such as dichloromethane and ethyl acetate), whereas more polar compounds (such as glycosides and polyphenols) will be concentrated in the more polar solvents (such as butanol or water). Fractionation as a secondary processing step applied to herbal extracts is described in section 3.4.

Separation techniques

After the completion of extraction, the liquid so obtained is separated from the marc by filtration through a filter cloth or filter-paper to remove any particulate insoluble residues. Other separation techniques, including decantation, centrifugation or straining, may be used depending on the method of extraction and composition of the matrix.

Concentration

The extract is often concentrated by the removal of excessive solvent to a thick concentrated extract or to a solid mass. The concentration procedures may involve evaporation under reduced pressure, freeze-drying or spray-drying.

3.2.3 Common herbal preparations obtained by extraction

The extraction process using suitable solvents can yield herbal extracts of liquid, semi-solid or solid consistency. There are four general categories of herbal extracts, i.e. liquid (fluid) extract, soft extract, oleoresin and dry extract.

3.2.3.1 Liquid (fluid) extract

Liquid (fluid) extract is a liquid preparation of herbal materials obtained using water, alcohol or other extraction solvents. Common preparations include:

- Fluidextract

Fluidextract is an alcoholic liquid extract produced by percolation of herbal material(s) so that 1 mL of the fluidextract contains the extractive obtained from 1 g of the herbal material(s).

- Decoction

Decoction is a water-based herbal preparation made by boiling herbal materials with water, and is commonly utilized in various traditional medicine contexts. In some cases, aqueous ethanol or glycerol can also be used to prepare decoctions. However, decoctions may be prepared by a programmable decocting machine that processes the herbal material at a specific temperature for a specific duration and then dispenses the decoction in hermetically sealed plastic pouches of a specified single-dosage volume that can be refrigerated for subsequent reheating and consumption. The amounts of herbal material and solvent used, as well as the length of the decocting process, should be specified.

- Infusion

Infusion is a dilute solution prepared by steeping the herbal materials in boiling water for a short time. Infusions prepared in edible oil or vinegar are also available.

- Tincture

As a general rule, a "tincture" is an alcoholic or hydroalcoholic extract of a herbal material, typically made up of 1 part herbal material and 5–10 parts solvent (for example, ethanol or wine). Tinctures can be prepared by extracting herbal materials usually with ethanol of a suitable concentration. The ratio of water to alcohol should be recorded.

- Macerate

Macerate is a liquid preparation prepared by soaking the herbal material(s), reduced to a suitable size, in water at room temperature for a defined period of time, usually for 30 minutes, when not otherwise specified.

3.2.3.2 Soft extract

Soft extract is a semi-solid preparation obtained by total or partial evaporation of the solvent from a liquid extract.

3.2.3.3 Oleoresin

Oleoresin is a semi-solid material composed of a resin in solution in an essential and/or fatty oil obtained by evaporation of the excess solvent.

3.2.3.4 Dry extract

Dry extract is a solid preparation obtained by evaporation of the solvent from a liquid/fluid extract. Dry extract can also be prepared by spray-drying with or without the use of an adsorbent (such as methyl cellulose), or by drying and milling to produce a powder. This may be further processed by compression or with use of a binding agent or granulation liquid to produce multiparticulate granules.

3.2.4 Factors influencing extraction of herbal materials

A number of factors influence the efficiency and reproducibility of the extraction process. Issues to consider include the solvent used to make an extract, particle size of the herbal material, the herb-to-solvent ratio, extraction process used (for example, percolation or maceration), extraction time, temperature and other relevant conditions. All these factors should be optimized and set out in the SOP, and be strictly adhered to.

3.2.5 Selection of extraction methods

- The choice of extraction method is governed by the nature (stability, solubility, structural complexity and other properties of the chemical constituents) and amount of material to be extracted. For large amounts, the feasibility of extracting on a bulk scale should be considered.
- The extraction method should be as exhaustive as possible, i.e. removing as much of the desired chemical constituent as possible from the plant matrix.
- It should be fast, simple, economical, environment-friendly and reproducible.

3.2.6 Extraction conditions and procedures

Solvent

- Depending on the nature of the target compounds or undesirable compounds, an appropriate solvent (or solvent mixture) should be selected. While water has been, and is, most commonly used as a solvent, organic solvents of varying polarities are often used in modern methods of extraction to exploit the various solubilities of phytochemical constituents. For example, an aqueous solution of alcohol (for example, 50–80% aqueous ethanol) can extract the majority of organic chemical constituents from herbal materials. Other solvents may apply for the extraction of specific types of constituents (such as proteins and polysaccharides).
- When selecting a solvent or solvent mixture, the following factors should be considered: solubility of the target compounds, stability and reactivity of the solvent, safety (low toxicity, low flammability, non-corrosiveness), cost, ease of subsequent solvent removal and solvent recovery (low boiling-point), and environmental friendliness.

- Before using a solvent, the safety data sheet[4] should be reviewed and appropriate protective measures should be implemented. Precautions must be taken to minimize the risk of fire and explosion. Care should be taken to reduce environmental contamination and to protect workers and other people in the vicinity from exposure to chemical hazards.
- Toxic solvents and those that are damaging to the environment, for example, benzene, toluene and carbon tetrachloride, should be avoided. Diethyl ether should also be avoided as it is highly flammable and can lead to the formation of explosive peroxides. The use of chlorinated solvents is discouraged; if used, dichloromethane is preferred to chloroform, the latter being more toxic. Ethanol is preferred over methanol; the latter has higher toxicity.
- Solvents are classified into three classes according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),[5] with respect to their potential risk as follows:
  - class 1 (solvents to be avoided such as benzene);
  - class 2 (limited toxic potential such as methanol or hexane); and
  - class 3 (low toxic potential such as ethanol) (*18*).
- Solvents of general-purpose grade available in plastic containers are often contaminated by plasticizers, and minimizing contamination is especially important when carrying out bulk extraction requiring large volumes of solvent. It is advisable to distil solvents prior to use.
- The amounts of solvent used must be optimized to ensure batch-to-batch conformity.
- The quality and specification of solvent used should be specified and controlled.
- Solvents should be properly stored in non-plastic containers in a well ventilated, fire and explosion containable area; and protected from direct exposure to sunlight.

[4] United Nations (2015) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Sixth revised edition. Available at: https://www.unece.org/trans/danger/publi/ghs/ghs_rev06/06files_e.html.

[5] International Council for Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use. ICH Harmonized Guideline – Impurities: Guideline for Residual Solvents (Q3C (R6) dated October 20, 2016). (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Q3C_R6__Step_4.pdf) accessed on 18 May 2017.

- When solvents are recycled, strength and purity must be confirmed prior to reuse. Recycled solvent should be used in the same extraction process only.
- Waste solvents must be disposed of safely and properly. National, local or institutional regulations on waste solvent disposal must be strictly followed.
- Limits for solvent residue in extracts or herbal preparations are important to observe especially when the solvent is not considered safe for general consumption.

Temperature

- To avoid thermal degradation of the chemical constituents, extractions are preferably performed at a temperature below 40 °C, unless evidence is available to support the use of higher temperatures.
- For heat-stable constituents, Soxhlet extraction or decoction can be used. In any case, higher than required temperatures should be avoided.
- Temperature during the entire extraction process should be controlled and recorded.

Length of treatment

- The length of extraction time depends on the purpose for which the extraction is performed and the nature of the active phytochemical constituents. Insufficient time will result in incomplete extraction, but prolonged extraction will lead to excessive extraction of the unwanted constituents and/or degradation of active chemical compounds.
- The number of repeated extraction cycles required for the complete removal of the desirable chemical constituents is as important as the length of time for each extraction.
- The length of extraction time and the number of cycles should be controlled and recorded.

3.3 Distillation

For the extraction of volatile components of herbal materials, such as essential (volatile) oils, the odorous and volatile principles of plants, techniques such as distillation, expression and enfleurage may be employed. Primary distillation

sometime takes place soon after the herb is harvested or collected to obtain crude oils. In other cases, herbal materials are distilled under well-controlled GMP conditions in the manufacturing facility.

Water or steam distillation is a method of choice for extracting volatile ingredients from herbs. In brief, the herbal material is packed in a still, a sufficient amount of water is added and brought to the boil (water distillation). Alternatively, a stream of steam is introduced to the herbal material that has been pre-soaked in water (water-steam distillation), or a stream of steam is introduced to herbal materials without water being added (direct steam distillation).

The method of distillation depends on the condition of the herbal materials. Water distillation can be applied to fresh herbs to avoid steam penetrating into the materials such as rose flowers, while direct steam distillation is often used for fresh or dried herbal materials. Freed from the plant tissue, the essential oil is carried away with the steam. Upon condensation, the water and oil are collected in liquid form, which then separates into two immiscible layers. During the process, the yield of essential oil can be quantified by using appropriate methods such as the Clevenger apparatus.

The yield and quality of essential oil obtained by distillation is affected by the process parameters. It is advisable to define optimal conditions in order to obtain the best results. Among the contributing factors are: mode of distillation, condition of raw herbal materials, loading of herbal materials, steam pressure and temperature and length of time for distillation.

3.3.1 Distillation procedures

- The distillation apparatus must be set up properly and safely according to the manufacturer's instructions.
- Distillation should be carried out in a well-ventilated room.
- Optimum distillation conditions, for example, heating rate, herb/solvent ratio and distilling rate, have to be specified and controlled.
- The equipment used should conform with the official safety standards and all procedures must be conducted in accordance with the operational instructions and safety requirements.
- The water used for distillation should at least comply with local requirements for drinking water.

3.3.2 Other methods

Volatile oils that may be decomposed during distillation can be obtained by expression (mechanical pressing), solvent extraction, supercritical carbon dioxide extraction or by the enfleurage process suitable for delicate flowers.

3.4 Fractionation

Fractionation is a separation process in which a mixture is divided into a number of smaller quantities (fractions) with higher content of target substances (chemical compounds). The crude extracts of herbal materials contain complex mixtures of chemical constituents with diverse chemical and physical characteristics. It is often desirable to divide the chemical constituents into different groups based on their similarities in terms of chemical and physical properties, such as a flavonoid- or alkaloid-rich fraction. Fractional separation of a herbal extract can be achieved by subjecting the extract to a variety of fractionation techniques such as liquid–liquid partition and various forms of chromatography. The method can be applied to produce preparations enriched in active compounds, or to remove inactive and/or toxic constituents.

3.4.1 Liquid–liquid partition

Herbal extracts may be fractionated by dissolving in a suitable solvent, if not already in liquid form, and partitioning with an immiscible liquid. One liquid phase is typically aqueous and the other is an organic phase such as dichloromethane or ethyl acetate. The chemical constituents will separate into the different liquid phases depending on their affinity according to the principle of "like dissolves like". Manipulations of the pH of the aqueous phase combined with liquid–liquid partitioning can also be employed to separate a herbal extract into basic, neutral and acid fractions.

3.4.2 Chromatography

Further refinement of the extract fractions can be achieved by various chromatographic techniques, of which column chromatography is most commonly employed, particularly in the preparative scale. Column chromatography can be carried out using materials based on different mechanisms. Common modes are adsorption, partition, size exclusion, affinity and ion-exchange. The most frequently used stationary phases (solvents) are silica gel and alumina in adsorption chromatography. In size-exclusion and ion-exchange chromatography, polymeric gels and ion-exchange resins, respectively, are used. A proper column packed with the appropriate stationary phase and eluted by a mobile phase with suitable elution power is crucial to obtain optimized separation of chemical constituents in the herbal extract.

The counter-current techniques, such as high-speed counter-current chromatography and droplet counter-current chromatography, which also employs a liquid–liquid partitioning mechanism, can also be applied to separating constituents in the herbal extract.

3.4.3 Fractionation procedures

Liquid–liquid partition

- The storage, use and disposal of solvents must be done with care and in conformance with the national, local and institutional regulations.
- Experimental procedures should be carried out in certified facilities with sufficient ventilation and safety measures. Ideally, they should be performed inside fume hoods.

Chromatography

- The choice of stationary phase depends on the polarity, molecular size or the charge of the desired ingredients. It should be supported by a good rationale.
- The choice of mobile phase (solvent system) must be optimized.
- Column operation and development procedures (for example, column length and inner diameter, amount of stationary phase used, column packing, particle or bead size or macropore size, porosity and surface area, phase and support, sample application, elution gradient formation, flow rate, temperature, fraction collection and detection method), should be specified and standardized.

3.5 Concentration and drying

The herbal extracts or fractions enriched in active ingredients are often reduced to produce a more concentrated liquid by the removal of excess solvent. This can be achieved through evaporation or vaporization. Solvent (single) can be recovered and may be reused provided that appropriate quality control is ensured. Mixed solvents are not reusable. The concentration depends on the desired end-product.

Equipment for concentration may include descending film, thin layer or plate concentrators. Any method used to concentrate the extracts must avoid excessive heat because the active ingredients may be heat labile. The liquid preparation so obtained may be used as it is or further processed into a semi-solid or dry extract.

When complete drying is required, the drying process can make use of vacuum freeze-dryers (lyophilizers), cabinet vacuum dryers, continuously operating drum or belt dryers, microwave ovens or atomizers. The choice of technique for drying depends on the stability of the product and the amount of solvent that must be removed. The total removal of solvent results in a dry

extract, which may be less susceptible to microbial contamination than liquid extracts. Dry extract powders are often produced by drying the extract onto an inert carrier, such as methyl cellulose, maltodextrin or another excipient fit for the intended purpose, to facilitate processing into the final finished product.

3.5.1 Concentration and drying procedures

- The minimization of loss and/or damage to the chemical constituents of interest is critical to ensuring the effectiveness of the preparation. Therefore, the preservation of the active ingredients is of paramount importance during the concentration stage when heat is often applied to evaporate the solvent. Any concentration process should ensure that minimal thermal decomposition and chemical reactions (such as oxidation) occur. For organic solvents, evaporation under reduced pressure at a temperature below 40 °C is preferred.
- Solvent removal should be done as soon as possible after extraction. Prolonged exposure to sunlight should also be avoided.
- While evaporation is the most common and the most often applied technique for concentration, other approaches such as membrane technology and freeze-drying concentration are available.

3.6 Fermentation

In some cases, a herbal preparation is obtained after undergoing a process of fermentation of the comminuted herbal material or decoction. Fermentation can be either natural ("self-fermentation") involving microbial cultures already present on the herb, enzymes naturally occurring in the herb (which may be activated by bruising the herb), or both, or by introducing an appropriate microbial organism (for example, *Lactobacillus* bacteria or yeast).

For natural fermentation, the dry comminuted herbal material, a decoction, or an extract of herbal material is often mixed with the juice of sugar-cane, brown sugar or honey and the mixture is kept in an airtight utensil for several weeks for anaerobic fermentation to occur.

In some cases, herbal materials are mixed with a small amount of water and shaped into bricks, followed by microbial cultivation in an incubation room for a week or so, letting the mould grow on the surface of the herbal materials.

3.6.1 Fermentation procedures

- When fermentation is required to produce a herbal preparation, all utensils should be completely cleaned. A non-corrosive fermenter is required.

- The water to be used should comply with local requirement for potable water, not be alkaline and should be free of inorganic matter (deionized water).
- The temperature and length of fermentation should be optimized and controlled.
- When fermentation is complete, the solution should be filtered and stored in suitable containers.

3.7 Advanced cutting and powdering

Cutting and powdering (or grinding) of the crude drug has many advantages as this process facilitates reduction of the plant material to a desirable particle size. During the post-harvest processing stage, primary cutting takes place to reduce the size of large pieces of herb to facilitate transportation and cleaning or washing. In many cases, herbal materials are further cut into small pieces of particular size and shape following traditional practice. In other cases, size reduction of the herbal materials facilitates the process of extraction and the preparation of dosage forms such as capsules. The ground powder is usually subjected to sieve analysis to achieve uniform distribution of a desired particle size. Various types of grinding machines can be utilized depending on the hardness, size, heat stability, friability and structural features of the plant part and output characteristics.

3.7.1 Procedures

The appropriate particle size of a comminuted herbal material depends on its nature and its subsequent processing. When a national pharmacopoeia defines approved size ranges, those standards should be followed. In general, for dried leaves, flowers and whole herbaceous plants, an average particle size of 5–10 mm is adequate for extraction, while for harder materials such as wood, bark, roots, rhizomes and seeds, 0.5–5 mm is recommended. In special cases, such as the extraction of specific alkaloids, 50–500 µm particle size may be desirable. For encapsulation of powders, a particle size of about 1–50 µm is usually required. Very fine powders (for example, nanoparticles) should be avoided for extraction because they have a tendency to block the filters. Nanoparticles may also be used for encapsulation.

Usually particle size reduction is carried out using mills with varying operational functions. Hammer mills are the most commonly used for initial size reduction. They are suitable for pulverizing roots, barks and stems, but not for grinding soft materials such as flowers and leaves. Other types of mills such as crusher mills are good for crushing fibrous herbal materials, and further size reduction can be achieved by using cutter mills or disc mills.

3.8 Processing documentation

The general principles for documentation are set out in the *Good manufacturing practices for pharmaceutical products: main principles* (*5*, *8*, *17*).

In addition to the data called for in the above guidelines, the documentation for herbal preparations should as far as possible include, as a minimum, the following information:

- botanical information as specified in section 2.5;
- batch number, batch size, and any other identification code;
- supplier;
- dates of receipt of the herbal material, processing of the material, and completion of the process;
- name of person in charge of the processing;
- name of quality assurance manager; and person in charge of batch release;
- previous processes that the herbal material has already undergone;
- characteristics of the herbal preparation (such as type of preparation, ratio of the herbal material to the herbal preparation, organoleptic characters);
- methods used for processing to produce herbal preparation;
- details of the procedures (master formula), including quantity of herbal materials, extraction solvent, additive, descriptions of the steps of operation, operational conditions used during the process, and other relevant information;
- weight or amount of the herbal preparation;
- batch production: give details of deviations or modifications of the master formula;
- quality control parameters (such as identification tests, tests on water content and impurities, residual solvents, microbial contamination tests, shelf life), acceptance limits of the tests and quantitative assay results of active ingredients, markers or chemical reference standard(s);
- storage conditions and containers; and
- shelf life and retest period.

An SOP including all processing steps should be adopted and documented in the Master Record. Batch records should be kept and any deviations from the SOP should be fully recorded and investigated. Name(s) of all operators, and the dates and time at which each step or stage are carried out should be documented.

4. Good herbal processing practices for the production of herbal dosage forms

4.1 General information

In contrast to synthetic pharmaceutical preparations, certain herbal materials and herbal preparations may undergo simpler good practice processes to become suitable dosage forms and final products for administration. However, these dosage forms should be produced under applicable GMP (*4–6*, *8*) conditions. Starting materials for the preparation and production of various herbal dosage/final dosage forms should consist of good quality medicinal plants cultivated or collected as prescribed by GACP (*1*). They should have been subjected to post-harvest processing, followed by further processing into herbal materials or herbal preparations under GHPP as described previously (sections 2 and 3).

Examples of a number of herbal dosage forms are presented in the *Japanese Pharmacopoeia*.[6]

The following describes some common dosage forms of herbal medicines. National and regional regulations and GMP guidelines must be followed for the production of finished products.

4.2 Preparation of liquid herbal dosage forms

Liquid herbal dosage forms as described here are oral preparations, including, but not limited to, the following product types or categories. These liquid herbal dosage forms may be prepared by dissolving the herbal preparation in an aqueous or non-aqueous solvent, by suspending it in an appropriate medium or by incorporating it into one of the two phases of an oil and water system.

4.2.1 Fluidextract

For description, see section 3.2.3.1

4.2.1.1 Preparation of fluidextracts

Fluidextracts are prepared by percolation of herbal material(s) using an aqueous alcoholic menstruum. After being thoroughly moistened, the mixture is packed firmly into a percolator and covered with additional menstruum. It is macerated for 24 hours, then percolated at a moderate rate, adding fresh menstruum as

[6] Ministry of Health, Labour and Welfare, Government of Japan, General Rules for Preparations – [4] Monographs for Preparations Related to Crude Drugs, *Japanese Pharmacopoeia 17th edition*, 2016. https://www.pmda.go.jp/files/000217650.pdf.

necessary to completion. The first 700–800 mL of the percolate should be reserved for use to dissolve the residue from the additional percolate that has been concentrated to a soft extract at a temperature not exceeding 60 °C. The extract is adjusted with menstruum, if necessary, so that it satisfies the requirements for content of solvent (in a ratio of one part (1.0 mL) of liquid to one part (1.0 g) of the herbal material). They may be filtered, if necessary.

4.2.2 Decoctions

For description, see section 3.2.3.1

4.2.2.1 Preparation of decoctions

In many traditional medicine contexts, decoctions are prepared by boiling the herbal materials in water for a certain period of time, after which they are strained and taken directly by the patients. The amounts of water used and the length of boiling are generally specified by the practitioners on a case-by-case basis.

4.2.3 Infusions

For description, see section 3.2.3.1

4.2.3.1 Preparation of infusions

Infusions are prepared by macerating the herbal materials for a short period of time with warm or boiling water.

4.2.4 Tinctures

For description, see section 3.2.3.1

4.2.4.1 Preparation of tinctures

Tinctures are usually prepared by either maceration or percolation, using ethanol, wine or a hydroalchoholic mixture to extract the herbal material, or by dissolving a soft or dry extract of the herbal material in ethanol of the required concentration. Tinctures are adjusted, if necessary, so that they satisfy the requirement for content of solvent (1 part of herbal material and 5–10 parts of solvent). They may be filtered if necessary.

4.2.5 Syrups

Syrups are viscous liquids containing sugars or other sweetening agents. They are prepared by dissolving, mixing, suspending or emulsifying herbal extracts or decoctions in a solution of honey, sucrose or other sweetening agents.

4.2.5.1 Preparation of syrups

Syrups are usually prepared by adding sucrose (at least 45% m/m) to the herbal solution or decoction, and then heating and straining it. Other polyol sweetening agents may be used. Sufficient purified water is then added to yield a product of the desired weight or volume. Syrups should be made in quantities that can be consumed within a reasonable period of time. If necessary, syrups may contain approved preservatives to prevent bacterial and mould growth.

4.2.6 Oral emulsions

Oral emulsions are preparations consisting of a two-phase system composed of at least two immiscible liquids such as oil-in-water preparations that are rendered homogeneous and stabilized by the addition of emulsifying agent(s). For example, an oil obtained from herbs (for example, castor oil) is dispersed in water and emulsified with an emulsifying agent such as gum acacia.

4.2.6.1 Preparation of oral emulsions

Various techniques can be applied to uniformly disperse one liquid in another immiscible liquid in the form of small droplets throughout the other. When emulsions are prepared, energy must be expended to form an interface between the oily and aqueous phases. Emulsification equipment includes a wide variety of agitators, homogenizers, colloid mills and ultrasonic devices.

4.2.7 Aromatic waters

Aromatic waters are water preparations saturated with essential oils or other aromatic or volatile substances. Aromatic waters have a characteristic odour of the essential oil or volatile substances used.

4.2.7.1 Preparation of aromatic waters

Usually, an essential oil (1 part) is shaken in recently distilled water (999 parts) and set aside for 12 hours or longer after mixing with 10 parts of talcum powder. The solution is filtered and made up to a certain volume with water. Aromatic waters will deteriorate over time due to volatilization, decomposition or mould growth. They should, therefore, be made in small quantities for immediate use and protected from intense light, excessive heat and stored in airtight, light-resistant containers, if necessary.

4.3 Preparation of solid herbal dosage forms

Solid dosage forms as described here are those that are most commonly found in herbal medicine, but they are not limited to the following categories.

4.3.1 Herbal tea bags

Herbal tea bags are used in many traditional medicine systems as a dosage form. Each tea bag contains ground herbal materials (a single herb or a mixture of different herbs) sufficient for one dose for making into an infusion.

4.3.1.1 Preparation of herbal tea bags

Herbal materials (for example, dried roots, leaves or flowers) are put into paper or cloth bags. Herbal tea bags should be free of bleach, gluten and dioxin. Metallic pins, used for attaching a piece of thread to the tea bag, should be avoided as this may release unsafe cations into the solution. When used, boiling water is poured into the vessel or cup containing the bag.

4.3.2 Plant powders

In many traditional medicine systems, ground powders of herbal materials are taken directly by patients as a dosage form. Powders are ground into various coarse or fine particle sizes, excluding nanopowder.

4.3.2.1 Preparation of plant powders

Powders are prepared by grinding or pulverizing dried herbal materials to a suitable particle size. When used, they are suspended in warm water ready for ingestion, or more commonly, they are packed into capsules or sachets.

4.3.3 Dry extract powders (powdered extracts)

Dry extract powders are solid preparations with a powdery consistency, obtained by evaporation of the solvent used for extraction. They may contain suitable added substances such as excipients, stabilizers and preservative, and suitable for incorporation into a dry formulation as in capsules, tablets or granules.

4.3.3.1 Preparation of dry extract powders (powdered extracts)

Dry extract powders are prepared by spray-drying or freeze-drying of a fluid extract with or without the use of an adsorbent (such as methyl cellulose), or by drying and milling to produce a powder. Excipients are often used for purposes such as improving taste or facilitating the packaging step.

4.3.4 Granules

Granules are dried liquid (fluid) extracts processed into spherical particles composed of agglomerations of smaller particles. Typically, granules are reconstituted to a suspension or solution by the addition of water to make a "herbal tea" for administration, although they can be administered directly. They are also used in tablet compression or capsule filling.

4.3.4.1 Preparation of granules

In the typical manufacture of granules, the dried liquid extract is blended with diluents, binders or other suitable excipients, then wetted with an appropriate binding solution or solvent to promote agglomeration. The composition is dried and sized to yield the desired material properties.

4.3.5 Pills

Pills are dry extract powders in the form of small, spherical solids, similar to, as a rule, but larger than granules (size may vary in different traditional medicine contexts). In certain traditional medicine context, pills are also made from powdered herbs/herbal materials.

4.3.5.1 Preparation of pills

Pills may be prepared by trituration of dried powdered herbs or dry extract powders with suitable powdered excipients in serial dilution to attain a uniform mixture. Liquid excipients that act to bind and provide plasticity are added to the dry materials, and kneaded to form a mass. Typically, pills are swallowed with warm water.

4.3.6 Capsules

Capsules are solid dosage forms in which the herbal substance is enclosed in either a hard or soft, soluble shell of gelatin or other suitable materials. Hard-shell capsules (also known as two-piece capsules) consist of two pieces (a body and a cap) in a range of standard sizes; soft-shell capsules (also known as one-piece or gel capsules) comprise an outer case encapsulating a liquid or paste. The exact composition of the capsule varies with the nature of the content.

4.3.6.1 Preparation of capsules

Capsules are prepared by enclosing a plant powder, or homogeneous dry extract powder or granules with excipients in a suitable capsule base such as gelatin, of a particular shape and size. In the case of gel capsules, liquid extract or soft extract can also be encapsulated. The process is carried out using specialized equipment.

4.3.7 Tablets

Tablets are solid preparations in which the herbal extract powder, plant powder or granule is blended with excipients and formed into a defined shape and size by compression.

4.3.7.1 Preparation of tablets

Tablets are usually prepared by mixing the homogeneous dry extract powder, plant powder or granules with excipients such as diluents and binders, followed by compression into a defined shape and size. Tablets may be coated or uncoated.

4.3.8 Lozenges

Lozenges (compressed lozenges are referred to as "troches") are solid dosage forms that are designed to dissolve slowly in the mouth to provide local action in the oral cavity or the throat, such as cough drops or pastilles, but may also provide systemic action. Lozenges often contain flavouring agents and sweetened bases.

4.3.8.1 Preparation of lozenges

In the typical preparation of lozenges, sucrose (or another excipient such as sorbitol) is cooked with the herbal extract and water. Flavouring and colouring agents are added and thoroughly mixed while cooling. Individual units of the desired shape are formed by filling the molten mass into moulds. Care should be taken to avoid excessive moisture during storage to prevent crystallization of the sugar base.

4.4 Preparation of other herbal dosage forms

4.4.1 Ointments, creams and salves

Ointments, creams and salves are topical preparations for application to the skin. They are usually semi-solid emulsions dissolved or dispersed in a suitable base. Salves are often solid at room temperature. They may contain emulsifiers or thickening agents.

4.4.1.1 Preparation of ointments, creams and salves

Ointments and creams can be formulated with a herbal extract or powder and a variety of oils and emulsifying agents. Preparation usually involves heating, mixing and stirring the lipid and aqueous portions until the mixture has congealed. They usually require the addition of preservative unless they are intended to be used within a relatively short period of time.

4.4.2 Inhalations

Inhalations are preparations intended for administration as aerosols to the bronchial tubes or lungs. They are usually either dry powder inhalers or inhalation liquid preparations. For administration of inhalations, suitable devices or apparatus are required. Steam inhalation of volatile substances from herbal teas or essential oils is used as a traditional inhalation method. The preparations

are also used at room temperature with suitable evaporating devices and as sticks when the volatile substance is incorporated in a suitable vehicle.

4.4.2.1 Preparation of inhalations

Dry powder inhalers are prepared by pulverizing dry extracts into fine particles. When necessary, lactose or other suitable excipients are added to make a homogeneous mixture. Inhalation liquid preparations are usually prepared by mixing dry herbal extracts with a vehicle and suitable pH-adjusting agents to make a solution or suspension. Suitable preservatives may be added to prevent the growth of microorganisms.

4.4.3 Plasters and patches

Plasters and patches contain herbal preparations such as dry or soft extracts on pieces of fabric or plastic elastomer sheets in such a way as to adhere to the skin and attach to the backing. When applied topically to the skin, they deliver the active ingredients through the skin to underlying tissues, usually for the relief of pain, backache or sore muscles.

4.4.3.1 Preparation of plasters and patches

A dry or soft extract of herbal preparation is spread uniformly on an appropriate support that is usually made of a rubber base of synthetic resin. Plasters are available in a range of sizes or cut to size to effectively provide prolonged contact with the site of application. They adhere firmly to the skin but can be peeled off without causing injury.

4.4.4 Medicated oils

Medicated oils are preparations formulated using fixed oils as base/vehicle where the prescribed herbal material, extract or fresh juice is mixed, macerated or boiled in oil. Different traditional methods are followed in the preparation of medicated oils but the aim is to obtain an oil enriched with fat-soluble extractives of the desired ingredients.

Medicated oils are mainly used topically, for example, in therapeutic massages and in certain cases, for oral administration.

4.4.4.1 Preparation of medicated oils

A fine paste of powdered herb or herbal material(s) together with a given media (if any, such as water, milk or fresh juices or decoctions of herbal materials) is mixed in a prescribed quantity of oil and macerated or boiled slowly with continuous stirring until complete removal of water or moisture (as the case may be). The oil is then decanted or strained while warm through muslin cloth and allowed to cool.

5. Technical issues supporting good herbal processing practices

In the formulation of a good practice protocol for herbal processing, a number of supporting technical measures must be considered and adopted. Since the primary objective is to produce quality processed herbal materials, herbal preparations and herbal dosage forms, many of the same technical issues associated with GACP, GMP and quality control (QC) methods are applicable to GHPP.

Therefore, these guidelines have been consulted for applicable good practice for adoption in GHPP. Moreover, the same technical issues relating to the post-harvest processing of cultivated and collected medicinal plant materials were addressed in section 4 of the *WHO guidelines on GACP for medicinal plants* (*1*). Likewise, the same technical issues relating to the processing of herbal materials and herbal preparations were described in the WHO guidelines on GMP for herbal medicines (*5*, *6*, *8*). Thus, the applicable good practice guidelines have been adopted in whole or in part, or modified as appropriate for the present guidelines.

5.1 Processing facilities

The ideal design and construction of a "post-herbal processing" facility incorporating the most appropriate location, buildings, herbal material handling and processing areas, water supply, effluent and waste disposal, changing facilities and toilets, hand-washing facilities in processing areas, disinfection facilities, lighting, ventilation, dust and storage of waste and unusable materials, have already been fully described in sections 4.1.5 (pages 19–23) of the *WHO guidelines on GACP for medicinal plants* (*1*). Therefore, they are adopted for the present guidelines and the descriptions are presented in Appendix 3 for easy reference.

Additionally, a facility for processing herbal preparations and herbal dosage forms would most appropriately be constructed following the principle of good manufacturing practice, as described in the *WHO guidelines on good manufacturing practice (GMP) for herbal medicines* (*5*). The relevant descriptions of such a facility are provided in Appendix 4 for easy reference.

5.2 Packaging and labelling

Processed herbal materials, herbal preparations and herbal dosage forms should be packaged as quickly as possible to preserve their quality. Packaging should prevent deterioration of the herbal medicines and they should be protected against exposure to pest infestations and other sources of contamination. When

applicable, the maximal holding time of the unpacked herbal medicines should be established.

Continuous in-process QC measures should be implemented to eliminate substandard materials, contaminants and foreign matter prior to and during the final stages of packaging. Processed herbal materials, herbal preparations and herbal dosage forms should be packaged in clean, dry boxes, sacks, breathable bags or other containers in accordance with the SOP and should comply with national and/or regional regulations of the producer and the end-user countries. Materials used for packaging should be non-polluted, clean, dry and undamaged, and should conform to the quality requirements for the processed herbal materials, herbal preparations or herbal dosage forms concerned. Fragile herbal materials should be packaged in rigid containers. Wherever possible, the packaging used should be agreed upon between the supplier and the buyer.

A label affixed to the packaging should include, but is not limited to, the following:

- accepted scientific name of the herb(s);
- official common name of the herb(s), herbal material(s), herbal preparation(s) or herbal dosage form(s);
- brand name of the herbal medicines (herb(s), herbal material(s), herbal preparation(s) or herbal dosage form(s));
- date of the processing of the processed herb(s), herbal material(s), herbal preparation(s), or herbal dosage form(s) obtained;
- processing techniques used;
- names and addresses of the herbal materials or herbal preparations processor, herbal dosage forms (finished herbal products) manufacturer, importer and/or distributor (i.e. the entity responsible for receiving consumer complaints and conducting a recall should the need arise);
- potency or strength of the active ingredient, if applicable (for example, for an extract the drug extract ratio of herbal material to extract, or the concentration of active or marker substance(s) used for standardization);
- net amount in the immediate container in terms of weight, measure or unit number;
- in the case of a finished herbal dosage form, the quantity of each active ingredient or marker per dosage unit;
- list of excipients;
- recommended storage conditions;

- batch number; and
- expiry date.

The label should also contain information indicating quality approval and compliance with national and/or regional labelling requirements.

Finished herbal product labelling should comply with the national/regional regulation/requirements.

Records should be kept of batch packaging, and should include the product name, place of origin, batch number, weight, assignment number and date. The records should be retained for a period of three years or as required by national and/or regional authorities.

5.3 Storage and transportation

All processed herbal medicines should be properly stored and preserved before use. They must be protected from microbial and insect contamination, as well as rodents and other pests. Every effort should be made to use the type of packaging that provides the best protection against physical damage to the processed materials; and at the same time to keep them away, as far as possible, from exposure to moisture, light, heat, insect and animal attack.

Rejected samples should be kept in a separate designated quarantined area, clearly labelled and with a specified handling period.

Toxic or controlled herbal materials or preparations should be checked, labelled and stored according to the government's regulations.

Storage areas should be of sufficient capacity to allow orderly storage of the various types of processed herbal materials, herbal preparations or herbal dosage forms with proper separation and segregation. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature and humidity limits. They should be controlled, monitored and recorded where appropriate to ensure good storage conditions, and comply with the "first-in and first-out" principle.

Conveyances used for transporting processed herbal medicines from the place of processing to the storage location should be clean and, where appropriate, well ventilated to maintain an appropriate airflow and to prevent condensation.

Pest infestation control in conveyances and in storage areas should be carried out by licensed or trained personnel. Only registered chemical agents authorized by the regulatory authorities of the source country and the countries of intended end-use should be used. All fumigation, fumigation agents and dates of application should be documented. When freezing or saturated steam is used for pest control, the humidity of the stored herbal medicines should be checked after treatment.

5.4 Equipment

All equipment, including tools and utensils used in the herbal processing procedures should be made of materials that do not transmit toxic substances, odour or taste; are non-absorbent; are resistant to corrosion and are capable of withstanding repeated cleaning and disinfection. The use of wood and other materials that cannot be adequately cleaned and disinfected should be avoided, except when their use would clearly not be a source of contamination. The use of metals known to cause corrosion should be avoided.

All equipment and utensils should be designed and constructed so as to prevent hygiene hazards and permit easy and thorough cleaning and disinfection. Where practicable, they should be accessible for visual inspection. Stationary equipment should be installed in such a manner as to permit easy access and thorough cleaning.

Containers for unusable materials or waste should be leak-proof, constructed of metal or other suitable impervious materials, should be easy to clean or be disposable, and should close securely.

All refrigerated spaces should be equipped with temperature measurement and recording devices.

5.5 Quality assurance and quality control

A quality assurance system is essential to ensure that herbal processing practice is consistently executed and controlled. The system for verification of compliance may differ from country to country. In general, compliance with quality assurance measures should be verified through regular internal oversight personnel (quality assurance manager) and external auditing visits to processing facilities by expert representatives of buyers and other stakeholders, and through inspection by national and/or local regulatory authorities. No processed herbal medicine should be released until its quality complies with or conforms to standard specifications.

5.6 Documentation

The SOPs should be adopted and documented. All methods and procedures used in the herbal processing and the dates on which they are carried out should be documented.

The types of information that should be collected include the items described in sections 2.5 and 3.8. Additionally, documentation on post-processing transportation and storage of processed products should be prepared.

Where applicable, the results of inspection should be documented in an inspection report, which contains copies of all documents, QC analysis reports, and local, national and/or regional regulations, and which are stored in compliance with their requirements.

5.7 Personnel

5.7.1 General

All personnel should receive proper training in post-harvest handling and herbal processing. Furthermore, all personnel required to handle chemical solvents and adjuvants should receive adequate training and possess sufficient knowledge of the appropriate techniques to be employed for their safe handling and proper use. Training records should be signed by the trainer and trainee and documented.

Local, national and/or regional regulations governing labour should be respected in the employment of staff for all phases of herbal processing.

5.7.2 Health, hygiene and sanitation

All personnel involved in the pre-herbal processing and during herbal processing procedures should be properly trained and should perform tasks in compliance with local, national and/or regional regulations on safety, materials handling, sanitation and hygiene.

All personnel should be protected from contact with potentially toxic or allergenic herbs by means of adequate protective clothing, including gloves and masks.

Health status

All new staff should pass a medical examination. No personnel known or suspected to be suffering from or to be a carrier of a disease or illness likely to be transmitted, should be allowed to enter any processing area, and should immediately be reported to the management, and suspended from work as deemed medically appropriate.

Health conditions that should be reported to the management for consideration regarding medical examination and/or possible exclusion from handling of herbal medicines and herbal processing, processed herbal medicines and associated equipment include but are not limited to: jaundice, diarrhoea, vomiting, fever, sore throat with fever, visibly infected lesions (boils and cuts, among other conditions) and discharges from the ear, nose or eye. Any personnel who have cuts or wounds and are permitted to continue working should cover their injuries with suitable waterproof dressings.

Personal hygiene and behaviours

Personnel engaged in herbal processing and who handle processed herbal medicines should be trained to maintain a high degree of personal cleanliness, and, where appropriate, wear suitable protective clothing and gloves, including head/hair covering and footwear.

Personnel should always wash their hands at the start of handling activities, after using the toilet, and after handling herbal processing and herbal medicines, or any contaminated material.

Smoking, drinking and eating should not be permitted in herbal processing areas.

Visitors

Visitors to processing and handling areas should wear appropriate protective clothing and adhere to all of the personal hygiene provisions mentioned above (WHO, 2003a).

6. Other relevant issues

6.1 Ethical and legal considerations

All herbal processing must be carried out in accordance with applicable legal and environmental requirements and with the ethical codes or norms of the community and country in which the activities take place.

6.2 Research, research training and information sharing

Research to understand and gain knowledge on the mechanism and scientific basis of processing procedures, such as traditional or historical methods is needed. It is also necessary to conduct research to find alternative processing procedures to achieve the same therapeutic effect as traditional or historical methods. Additionally, research to determine the chemical conversion process and mechanism involved in the qualitative and quantitative alteration of the biologically active chemical constituents following processing is needed and encouraged.

Technical information resulting from research on processing methods is useful for promoting technical advancement, and should be shared through publication, conferences or otherwise conveyed to interested stakeholders.

As in all technical endeavours, education and research training are essential to preserve technical expertise and to promote innovation in development of new and better techniques and procedures in herbal processing.

Research to develop GHPP for individual herbs or herbal materials and to document each in a monograph is strongly encouraged.

6.3 Adoption of good herbal processing practices

Member States or nations that have not adopted GHPP for herbal medicines are encouraged to establish or adopt such practices as part of quality assurance and control measures, as well as a part of their regulatory requirements for herbal medicines.

6.4 Intellectual property rights and benefits-sharing

Agreements on intellectual property rights and the return of benefits and compensation for the use of source herbal materials or herbal preparations concluded in writing by the sourcing contractor, shall be acknowledged and followed by the processor as appropriate (for example "Aichi Protocol" under the framework of the United Nations Convention on Biodiversity).

6.5 Threatened and endangered species

When obtaining herbs or herbal materials that are protected by national and international laws, such as those listed in national "red" lists, for processing, the processor shall ascertain and obtain appropriate documentation from the sourcing contractor that said materials were acquired only by relevant permission according to national and/or international laws, and that the provisions of the Convention on International Trade in Endangered Species of Wild Fauna and Flora have been complied with.

6.6 Safety management of toxic herbs

Among the herbal medicines (and their source medicinal plants) being used in traditional medicine contexts in different parts of the world, some are known to contain toxic substances that may lead to severe side-effects or even death. In general, these toxic herbal materials and their preparations or dosage forms have narrow therapeutic windows between effective dose and lethal dose. Examples of such toxic/effective therapeutic agents are cardioactive herbal preparations such as *Powdered Digitalis* and *Digitalis Capsules*, which at the proper dosages, are excellent therapeutic cardiotonic agents, but are lethal when an overdose is taken.

In order to safeguard the use of these potentially toxic herbs, special attention and safety management measures are required, for example:

- they must go through proper processing procedures for the purpose of neutralizing the toxicity or reducing the side-effects prior to use.
- They must be used under stringent measures of control and supervision by qualified and/or trained personnel.
- When poisoning and/or accidents related to the use of these toxic herbs occur, proper medical treatment should be given immediately.
- Member States should promote and ensure the safe use of potentially toxic herbs and their preparations.
- Member States are encouraged to establish national policies to achieve effective control of herbal safety and to strengthen risk assessment and management.

- Member States are encouraged to develop their own standards and guidelines for the use of potentially toxic medicinal plants.

References

1. WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva: World Health Organization; 2003.
2. WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues. Geneva: World Health Organization; 2007.
3. WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines. In: WHO Expert Committee on Specification for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 1 (WHO Technical Report Series, No. 1003).
4. WHO good manufacturing practices (GMP): supplementary guidelines for the manufacture of herbal medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 3 (WHO Technical Report Series, No. 937).
5. WHO guidelines on good manufacturing practices (GMP) for herbal medicines. Geneva: World Health Organization; 2007.
6. WHO good manufacturing practices (GMP): supplementary guidelines for the manufacture of herbal medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 2 (WHO Technical Report Series, No. 1010).
7. Quality control methods for herbal materials. Geneva: World Health Organization; 2011.
8. Good manufacturing practices for pharmaceutical products: main principles In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
9. Safety issues in the preparation of homeopathic medicines. Geneva: World Health Organization; 2009.
10. The International Pharmacopoeia, seventh edition. Geneva: World Health Organization; 2017.
11. WHO monographs on selected medicinal plants, volume 1. Geneva: World Health Organization; 1999.
12. WHO monographs on selected medicinal plants, volume 2. Geneva: World Health Organization; 2002.
13. WHO monographs on selected medicinal plants, volume 3. Geneva: World Health Organization; 2007.
14. WHO monographs on selected medicinal plants, volume 4. Geneva: World Health Organization; 2009.
15. WHO monographs on selected medicinal plants commonly used in the Newly Independent States (NIS). Geneva: World Health Organization; 2010.
16. General guidelines for methodologies on research and evaluation of traditional medicine Geneva: World Health Organization; 2000 (WHO/EDM/TRM/2000.1).

17. Good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report. Geneva: World Health Organization; 2003: Annex 4 (WHO Technical Report Series, No. 908).

18. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-first report. Geneva: World Health Organization; 2007: Annex 3 (WHO Technical Report Series, No. 943).

Appendix 1

Example of a model format for a good herbal processing practices monograph/standard operating procedure protocol to produce a herbal material

TITLE of the monograph/protocol

Processing of (name of the plant) *(Scientific name of the medicinal plant; medicinal plant part)*

1. **Objective of the standard operating procedure (SOP) protocol**

2. **Scope**

3. **Procedures**

3.1 **Sampling**

Sampling of herbal materials should follow applicable national or regional specifications. In absence of appropriate specifications, the following method may be considered: When a batch consists of five containers or packaging units, take a sample from each one. From a batch of 6–50 units, take a sample from five. In the case of batches of over 50 units, sample 10%, rounding up the number of units to the nearest multiple of 10 (WHO, 2011).

Quality testing of the raw material

Perform morphological identification/validation by macroscopic, microscopic or phytochemical and/or genomic identification/examinations and physicochemical tests by following the procedures set out in the national pharmacopoeia or other documents.

The following requirements must be fulfilled.

- Morphology: conform with the national pharmacopoeial or other relevant standards
- Identification (including macroscopic, microscopic examination, phytochemical and/or genomic identification/examinations, and/or chromatographic tests): conform with the pharmacopoeial standards
- Water content: ≤ xxx %

- Total ash: ≤ xxx %
- Acid-insoluble ash: ≤ xxx %
- Extractive: ≥ xxx %

3.2 Quality control assay

3.2.1 Marker compound(s)

Compound "Z" is used as the marker compound for plant X..y.. for quality control purpose. Obtain analytical grade Compound Z (≥ 98% purity) from a reliable source to serve as chemical reference substance.

3.2.2 High-performance liquid chromatographic analysis

Set up the high-performance liquid chromatography (HPLC) system. Perform system suitability test to ensure suitability of the instrument and method.

Under the recommended HPLC conditions, establish calibration curves by injecting an appropriate amount of the chemical reference (marker) standard solution in a series of concentrations.

Obtain HPLC chromatogram of the herbal material. Identify the analyte signal in the chromatogram by comparing the retention time with that of the peak of the chemical reference substance obtained under same HPLC conditions.

Calculate the percentage content of the analyte in the sample using the calibration curve.

Determine the percentage content of the marker compound again after final drying of the processed herbal material (section 3.10 below).

The following requirement must be fulfilled.

- Content of Compound Z before processing: ≥ xxx % calculated with reference to the dry weight of the starting material
- Content of Compound Z after processing: ≥ xxx % calculated with reference to the dry weight of the processed material

3.3 Testing of the excipient*

(**This step is not required if excipient(s) are not employed in the processing protocol*)

Perform tests by following the procedures set out in the SOP document. The following requirements must be fulfilled.

- Appearance: conform with internal standards
- Total excipient content: ≥ xxx %

3.4 Initial sorting of herb for processing

The source herbs are manually sorted by trained personnel according to the requirements specified in the SOP. Impurities (for example, dirt and non-medicinal plant parts) should be removed, and any materials of non-uniformed sizes should be excluded.

The following requirements must be fulfilled.

- Impurity: ≤ xxx %
- Size uniformity: ≥ xxx %
- Total recovery: ≥ xxx % (Recovery = Weight after sorting/Weight before sorting X 100%)

3.5 Washing

Washing should be performed by following the procedures set out in the SOP document. Pay attention to the quality of water used, the length of washing time, and any precautions applicable to the specific herb.

The following requirements must be fulfilled.

- Appearance after washing: in conformance with the SOP standard
- Recovery: xxx-xxx % (Recovery = Weight after washing/Weight before washing X 100%)

3.6 Steaming (or other treatment)

The procedures set out in the SOP document should be strictly followed. All equipment should be properly maintained, clean and performing at optimal and safe conditions.

The following requirements must be fulfilled.

- Appearance after steaming/treatment: in conformance with the SOP standard
- Recovery: ≥ xxx % (Recovery = Weight after steaming/Weight before steaming X 100%)

3.7 Semi-drying

If required, dry the samples according to SOP guidelines, either by sunlight or by artificial heating.

The following requirements must be fulfilled.

- Appearance after semi-drying : in conformance with the SOP standard

- Recovery: xxx-xxx% (Recovery = Weight after drying/Weight before drying × 100%)

3.8 Cutting/sectioning/comminuting

The processed material should be comminuted into the required size and shape in conformance with the SOP.

The following requirements must be fulfilled.

- Non-conforming pieces: ≤ xxx %
- Powder fineness:
- Recovery: ≥ xxx % (Recovery = Weight after cutting/Weight before cutting × 100%)

3.9 Final drying of processed herbal material

The cut materials should be thoroughly dried according to the SOP requirement.

The following requirements must be fulfilled.

- Water content of the final product: xxx-xxx %
- Recovery: ≥ xxx % (Recovery = Weight after drying/Weight before drying × 100%)

3.10 Final sorting

The dried material should be carefully inspected by trained personnel, with impurities removed and sorted into specific grades in accordance with the pharmacopoeial or trading standard.

The following requirements must be fulfilled.

- Impurity: ≤ xxx %
- Grade-1 pieces: ≥ xxx%
- Grade-2 pieces: xxx –xxx%
- Recovery: ≥ xxx % (Recovery = Weight after sorting/Weight before sorting × 100%)

3.11 Packaging, labelling and storage

3.11.1 Packaging

Processed materials should be packaged quickly and appropriately in appropriate, non-corrosive containers, and protected from light to preserve quality, prevent deterioration and to protect against contamination.

3.11.2 Labelling

Labels affixed to each package should clearly indicate the scientific name of the medicinal plant, the plant part, the processing method, the date of processing, the batch number, quality specification and compliance, quantitative and other relevant information, in compliance with the national/regional requirements.

3.11.3 Storage

The packaged products must be stored in a clean, dry and well-ventilated area, at a temperature appropriate for the proper maintenance of the final product, and protected against microbial and other sources of contamination and free from insects and animal pest attacks.

Appendix 2

Example of a model format for a good herbal processing practices monograph/standard operating procedure protocol to produce a herbal preparation or herbal dosage form

TITLE of the monograph/protocol

Processing of (name of the plant) *(Scientific name of the medicinal plant; medicinal plant part)*

1. Objective of the standard operating procedure protocol

The objective of this protocol is to establish a procedure for preparation of the finished product.

2. Scope

This procedure applies to processes required in the preparation of the fluidextract of the herbal material from *X*…*y*...

3. Procedures

This protocol should be carried out in accordance with the standard operating procedures (SOP) for the processing of material *X*…*y*... as described in this document, the SOP for equipment operation and maintenance, as well as those for facility management and cleaning. Any other relevant requirements may also apply.

The protocol should be adhered to in conjunction with relevant internal standards of the processing facility.

After the completion of each processing step, the products should be inspected by qualified personnel. All inspection records should be properly filed and retained for a period of three years or as required by national and/or regional authorities.

4. Herbal material

The identity of the herbal material should be confirmed using morphological identification/validation by macroscopic and microscopic examinations, as well as by using phytochemical and/or genomic identification/examinations, and

physicochemical tests by following the procedures set out in the pharmacopoeia or other documents.

Specifications such as those below should be in place.

- **Origins of the herb (natural state/cultivation):** Describe appropriate origins of the herbal material
- **Plant part:** Describe the desired plant part (i.e. flower)
- **Harvest/collection time:** Describe the appropriate months for harvest/collection (for example during flowering (June-July))
- **Processing:** Describe the processing of the herbal material
- **Drying conditions:** Describe the process for drying, if applicable
- **Purification:** Describe the process for inspection and removal of impurities
- **Storage conditions:** Specify the storage conditions. In general, the herbal material should be stored in a clean, dry and well-ventilated area, at a constant, appropriate temperature, protected against microbial and other sources of contaminations, free from attack by insects and animal pests
- **Transportation conditions:** Commercial vehicles should be clean, dry, deprived of any foreign matter. Conditions should ensure protection against moisture and contamination. Baskets, chests and jute bags can be used as containers. Each container should be labelled with the name of the material, date of harvest/collection, harvesting/collection site, net and gross weight and the name of the supplier

5. Processing

Descriptions of the herbal processing facility requirements should be maintained, i.e. certification of the site as a good practice facility. Details are given here for the raw components to be used in the production of the final herbal preparation.

As an example, raw *X...y...* herbal material to be processed into *X...y...* juice are detailed in the table below. In this example, the herbal material is extracted using ethanol 95% (V/V) and water as needed. The drug extract ratio is 1:1.

Raw material components in the production of *X...y...*juice

Raw materials	Function	Amount per 100 kg	Standard
Fresh *X...y...* herb	Herbal material	100.0 kg	Standard specification
Ethanol 95%	Extraction solvent	xx litres	Pharmacopoeia .XYZ
Extraction water	Extraction solvent	*quantum satis*	Pharmacopoeia .XYZ

Raw materials accepted for processing must meet specifications for identity and quality. Specifications include appearance/description of the herbal material, water content, total ash, as well as appropriate chemical assays. These criteria may follow criteria detailed in pharmacopoeial monograph(s).

- The steps below describe the preparation of the juice of *X..y..*:
- Step 1. The fresh fragmented herbal material is stabilized with the vapours of boiling 95% ethanol in an autoclave. The duration, temperature and vapour pressure are specified in the SOP. When the process is completed, the fluid separates from the herbal material.
- Step 2. The stabilized herbal material is placed in a macerator with post-stabilization fluid and water. The maceration process lasts for a period of time (n days) specified. At the end of the extraction process, the extract is separated from the solid materials in a manner specified by the SOP. The ethanol content of the extract and density of the extract are specified.
- Step 3. The resulting extract is stored in a stainless steel container for a minimum time (days/weeks) specified. The process ensures sedimentation of inorganic residual waste.
- Step 4. The extract is filtered using a pressurized process. The filter size and input pressure are selected as specified by the manufacturer or manufacturer's catalogue of the filtering unit.

6. In-process controls

Controls for tests conducted during the process should be described. A description of the tests, their methods and the acceptance criteria should be given. These include appearance (i.e. colour), particle size (amount expected to pass through a specified sieve size), water or alcohol content, and/or relative density.

7. Herbal dosage form

The herbal dosage forms may include extracts, pills, spirits, infusions, decoctions, teabags, tinctures, aromatic waters and fluidextracts (see footnote[1]).

8. Release specifications of final product

Identify criteria must be met for release of the final product. These criteria generally include appearance, organoleptic characteristics, relative density,

[1] A herbal preparation or a specific dosage form, as indicated above, can be prepared as per established pharmacopoeial methods.

chemical identity including specified quantities for chemical constituent(s), as well as limits for heavy metals, microbial contamination and residual matter.

- Chemical profile: i.e. TLC/HPLC fingerprint of chemical constituents
- Pharmacopoeial/standard quantitation of chemical markers, where applicable
- Heavy metals: limits defined
- Microbial: limits defined
- Residuals: limits for pesticides, fertilizers, foreign matter, solvent residue, mycotoxins, etc.

9. Certificate of analysis

A certificate of analysis should be generated following completion of quality control testing. This document should include the assay methods as well as the results obtained using those methods.

10. Packaging

The appropriate packaging of the containers should be described. Processed materials should be packaged quickly and appropriately in airtight, non-corrosive containers, and protected from light to preserve quality, prevent deterioration and to protect against contamination.

11. Labelling

Labels affixed to each package should clearly indicate the scientific name of the medicinal plant, the plant part, the herbal processing method, the date of processing, the batch number, quality specification and compliance, quantitative and other relevant information, in compliance with the national/regional requirements.

12. Storage conditions

The packaged products must be stored in a clean, dry and well-ventilated area, at a temperature appropriate for the proper maintenance of the final product, and protected against microbial and other sources of contaminations and free from insects and animal pest attacks.

13. Stability

Stability testing should be conducted to determine an appropriate shelf life.

14. Retained samples

Sufficient materials (raw material and finished goods) must be retained in proper storage conditions to allow for future verification of identity and quality.

Appendix 3

Processing facilities for post-harvest processing

The following is extracted from section 4.1.5 of the *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (WHO, 2003) (pages 19–23).

Processing facilities

In constructing or designing a processing facility, the following elements should be considered that will allow the establishment of a quality assurance system adaptable to the different types and steps of processing to yield the desired end-products.

Location

Facilities should preferably be located in areas that are free from objectionable odours, smoke, dust or other contaminants and are not subject to flooding or other natural adverse conditions.

Buildings

Buildings should be of sound construction and maintained in good repair. Filthy areas must be isolated from clean processing areas. All construction materials should be such that they do not transmit any undesirable substance including toxic vapours to medicinal plant materials. Electrical supply, lighting and ventilation should be appropriately installed.

Buildings should be designed to:

- provide adequate working space and storage room to allow for satisfactory performance of all operations;
- facilitate efficient and hygienic operations by allowing a regulated flow in processing from the arrival of the raw medicinal plant materials at the premises to the dispatch of the processed medicinal plant materials;
- permit appropriate control of temperature and humidity;
- permit control of access to different sections, where appropriate;
- permit easy and adequate cleaning and facilitate proper supervision of hygiene;

- prevent the entry of environmental contaminants such as smoke, dust, the entrance and harbouring of pests, livestock and domesticated animals;
- where appropriate, prevent direct sunlight from entering a particular section.

Medicinal plant material handling and processing areas

The layout and design of the work area should be such as to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, and otherwise avoid any adverse effect on the quality of the processed product.

- Windows and other openings should be constructed so as to avoid accumulation of dirt, and where appropriate, those that open should be fitted with insect-proof screens. Screens should be easily removable for cleaning and kept in good repair. Internal window sills, if present, should be sloped to prevent use as shelves.
- Doors should have smooth, non-absorbent surfaces and, where appropriate, be self-closing and close-fitting.
- Overhead structures and fittings should be installed in such a manner as to avoid contamination of medicinal plant materials (both raw and processed) by condensation and drippings, and should be protected to prevent contamination in case of breakage. They should be insulated, where appropriate and be designed and finished so as to prevent the accumulation of dirt and to minimize condensation, mould development and flaking. They should be easy to clean.
- Food preparation and eating areas, changing facilities, toilets should be completely separated from and not open directly onto medicinal plant material processing areas.

Water supply

- An ample supply of potable water, under adequate pressure and at suitable temperature, used for processing medicinal plant materials, should be available with appropriate facilities for its storage, where necessary, and distribution with proper protection against contamination.
- Ice should be made from potable water; it should be manufactured, handled and stored so as to protect it against contamination.

- Unless there is a post-water filtration or treatment system, non-potable water used for steam production, refrigeration, fire control and other similar purposes not connected with processing should be carried in completely separate pipes, identifiable preferably by colour and with no cross-connection with or back siphonage into the system carrying potable water.

Effluent and waste disposal

Facilities should have an effective effluent and waste disposal system, which should at all times be maintained in good order and repair; and should be constructed so as to avoid contamination of potable water supplies.

Changing facilities and toilets

Adequate, suitable and conveniently located changing facilities and toilets should be provided. Hand-washing facilities with warm or hot and cold water, a suitable hand-cleaning preparation and hygienic means of drying should be provided adjacent to toilets and located so that employees have to pass them when returning to the processing area. Notices should be posted directing personnel to wash their hands after using the toilet.

Hand-washing facilities in processing areas

Adequate and conveniently located facilities for hand-washing and a hygienic means of drying should be provided whenever the process demands. Where appropriate, facilities for hand disinfection should also be provided.

Disinfection facilities

Where appropriate, adequate facilities for cleaning and disinfection of working implements and equipment should be provided. These facilities should be constructed of corrosion-resistant materials, should be easy to clean, and should be fitted with hot and cold water supplies.

Lighting

Adequate natural or artificial lighting should be fitted throughout the facility. Where appropriate, the lighting should not alter colours of the medicinal plants undergoing processing.

Ventilation

Adequate ventilation should be provided to prevent excessive heat, steam condensation and dust and to remove contaminated air from both the processing and storage areas/facilities.

Storage of waste and unusable materials

Facilities should be provided for the storage of waste and unusable materials prior to removal from the premises.

Appendix 4

Processing facilities for production of herbal preparations and herbal dosage forms

The following is extracted from section 12 of the WHO guidelines on good manufacturing practices (GMP) for herbal medicines (WHO, 2007a) (pages 41–44).

Premises

In principle, the premises must be located, designed, constructed, adapted and maintained for the suitable processing/production operations to be performed.

General

In general, the layout and design of the facility must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of the end-products.

- Where dust is generated (for example, during sampling, weighing, mixing and process operations, packaging of powders), measures should be taken to avoid cross-contamination and facilitate cleaning.
- The facility should be situated in an environment that, when considered together with measures to protect the processing/manufacturing process, presents minimum risk of causing any contamination of materials or products.
- The facility should be situated in an environment that, when considered together with measures to protect the processing/manufacturing process, presents minimum risk of causing any contamination of materials or products.
- The facility used for the processing of herbal preparations or manufacture of finished products should be suitability designed and constructed to facilitate good sanitation.
- It should be carefully maintained, and be ensured that repair and maintenance operations do not present any hazard to the quality of products.
- It should be cleaned and, where applicable, disinfected according to written procedures, and records maintained.

- Electrical supply lighting, temperature, humidity and ventilation should be appropriate so that they do not adversely affect, directly or indirectly, the herbal products during their processing/manufacturing and storage, or the functioning equipment.
- It should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals.
- It should be designed to ensure the logical flow of materials and personnel.

Ancillary areas

- Rest and refreshment rooms should be separated from processing/manufacturing and control areas.
- Facilities for changing and storage of clothes, for toilet and washing purposes should be accessible for users.
- Maintenance workshops should be separated, if possible, from production areas or tools kept in rooms or lockers.
- Animal houses should be well isolated from other areas, with separate entrance and air handling facilities.

Storage areas

- Storage areas should be of sufficient capacity to allow orderly storage of various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished/processed products, products in quarantined and released, rejected, returned or recalled.
- Storage areas should be designed or adapted to ensure good storage conditions. They should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special conditions (for example, temperature and humidity) are required, they should be provided.
- Receiving and dispatch areas should be separated and protect materials and products from weather; and should be designed and equipped to allow containers to be cleaned if necessary.
- Where quarantine status is ensured by storage in separate areas, they must be clearly marked and access restricted to authorized personnel.
- Segregation should be provided for the storage of rejected, recalled or returned materials or products.

- Highly active and radioactive materials, narcotic and other dangerous materials presenting special risks, fire or explosion, should be stored in safe and secure areas.
- Printed packaging materials are considered critical to the conformity of the processed material/product to its labelling, and special attention should be paid to sampling and the safe and secure storage of these materials.
- There should be a separate sampling area for starting materials.

Weighing areas

- The weighing of starting materials and the estimation of yield by weighing should be carried out in separate areas designed for that use.

Production areas

- In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the processing or manufacture of particular herbal preparations/products, such as toxic and/or rare materials/products.
- Premises should be laid out as to allow the production to take place in such a way as to allow the processing/production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different herbal preparations/products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any manufacturing or control steps.
- Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces of the facility should be smooth and free from cracks and open joints.
- Pipe work, light fittings ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean.
- Drains should be of adequate size and designed and equipped to prevent back-flow.

- Production areas should be effectively ventilated, with air control facilities appropriate to the herbal material/product handled, to the operations taken and to the environment. These areas should be regularly monitored during both processing/production and non-production/non-production periods to ensure compliance with their designed specifications.
- Premises for the packaging of processed/finished products should be specifically designed and laid out so as to avoid mix-ups or cross-contaminations.
- Production areas should be well lit, particularly where visual on-line controls are carried out.

Quality control areas

- Quality control laboratories should be separated from production areas.
- Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient spaces should be given to avoid mix-ups and cross-contaminations. There should be adequately suitable storage space for samples, reference standards (in appropriate storage facility), solvents, reagents and records.
- The design of the laboratories should take into consideration the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and processing/production areas.
- Instruments should be housed in a separate room to protect them against electrical interference, vibration, contact with moisture and other external factors, or where it is necessary to isolate the instruments.