Revised Draft:

WHO guidelines on good herbal processing practices (GHPP) for herbal medicines

REVISED DRAFT FOR COMMENTS

Please address any comments on this revised draft WHO guidelines by 31 May 2017, to:
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TITLE: R-Draft: WHO guidelines on good herbal processing practices (GHPP) for herbal medicines – Revised draft for comments, March 2017

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### SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DRAFT DOCUMENT:

**WHO GUIDELINES FOR GOOD HERBAL PROCESSING PRACTICES FOR HERBAL MEDICINES**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date/Year</th>
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<tr>
<td>Need for a WHO technical guidance on processing to produce herbal materials, and to produce herbal preparations for quality control of herbal medicines at different stages of their production, was stated during the WHO informal meeting on methodologies for quality control of finished herbal products (Ottawa, Canada) as a recommendation to WHO for development/action.</td>
<td>July 2001</td>
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<tr>
<td>Reported to the 37th session of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), Geneva, on the output of the WHO informal meeting (July 2001) and informed the Committee that WHO planned to develop new technical guidelines on processing of herbal medicines; the Committee noted the proposal.</td>
<td>22-26 October 2001</td>
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<td>Needs for good processing practices for herbal medicines were also stated during the International Conferences of Drug Regulatory Authorities (ICDRAs)</td>
<td>Hong Kong SAR, China, November 2002, Madrid, Spain, February 2004</td>
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<tr>
<td>Drafting of the proposal on the development of WHO guiding document on good processing practices for medicinal plant materials</td>
<td>2003</td>
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<td>Obtained WHO’s internal approval in developing a WHO guiding document on good processing practices for medicinal plant materials (title: tentative)</td>
<td>November 2003</td>
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<td>Identification, collection, collation and compilation of technical information and reference materials for formulating draft synopsis and annotated content table</td>
<td>2008</td>
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<td>Development of concept paper on scope and background as well as the document development plan</td>
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<td>Further identification, collection, collation and compilation of technical information and reference materials for revising draft synopsis and annotated content table.</td>
<td>2012</td>
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<td>Revision of draft concept paper on scope and background as well as the document development plan</td>
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<td>Revision and elaboration of the draft synopsis and content table for drafting the first working draft guidelines</td>
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<td>Meeting proposal development and search for potential host of the meeting (2nd WHO consultation on quality control of herbal medicines)</td>
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<td>Further collection and collation of technical information and reference materials for the preparation of the first working draft guidelines</td>
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<td>Formulating the first working draft WHO guidelines on good processing practices for herbal medicines</td>
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<td>Formation of initial drafting group</td>
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<td>Reported on the progress to the 49th session of the WHO ECSPP, Geneva, October 2014</td>
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<td>Distribution of the first working draft WHO guidelines to the participants of the 2nd WHO consultation on quality control of herbal medicines for discussion at the 2nd WHO consultation meeting</td>
<td>October – November 2014</td>
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<td>Reported on the progress to the 37th Annual meetings of national centres participating in the WHO international drug monitoring programme, Tianjin, China, October 2014</td>
<td>October 2014</td>
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<td>At the 2nd WHO consultation meeting held in Hong Kong SAR, China, in November 2014, the first working draft WHO guidelines on good processing practices for herbal medicines were reviewed and discussed; and the objectives, scope and proposed contents were discussed intensively, and agreed. The draft synopsis and table of content of the proposed guidelines were further refined and agreed; it was also agreed to revise the first working draft WHO guidelines based on the discussion and agreed guidelines’ objectives, scope, and contents at the 2nd WHO consultation meeting.</td>
<td>17-19 November 2014</td>
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<td>Reported on the progress of the guidelines development at the 7th annual meeting of International Regulatory Cooperation for Herbal Medicines (IRCH), Lisbon, Portugal, December 2014</td>
<td>December 2014</td>
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<tr>
<td>Further identification, collection and collation of relevant technical information for revision of the first working draft guidelines</td>
<td>2015 – 2016</td>
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<td>Revision of the first working draft WHO guidelines</td>
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<td>Reported on the progress at the 8th annual meeting of IRCH, Riyadh, Saudi Arabia, December 2015</td>
<td>8-10 December 2015</td>
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<td>Formulation of the draft WHO guidelines on good herbal processing practices for herbal medicines for a global review</td>
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<td>Reported on the progress to the 51st session of the WHO ECSPP, Geneva, October 2016</td>
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<td>Reported on the progress at the 9th annual meeting of IRCH, New Delhi, India, November 2016</td>
<td>9-11 November 2016</td>
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<td>First global review on the draft WHO guidelines on good herbal processing practices for herbal medicines</td>
<td>December 2016 – February 2017</td>
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<td>Meeting proposal development and search for potential host of the meeting (3rd WHO consultation on quality control of herbal medicines)</td>
<td>December 2016 – February 2017</td>
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<tr>
<td>Compilation of comments received and revision of the draft</td>
<td>February – March 2017</td>
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<td>The second global review on the revised draft</td>
<td>April – May 2017</td>
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<tr>
<td>Compilation of comments received and revision of the revised draft (to form the 2nd revised draft)</td>
<td>June – July 2017</td>
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<td>Review and discussion of feedback received on the 2nd revised draft at the 3rd WHO consultation on quality control of herbal medicines, Hong Kong SAR, China, September 2017</td>
<td>4-6 September 2017</td>
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<td>Finalization of the manuscript based on the discussion at the 3rd WHO consultation meeting</td>
<td>September 2017</td>
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<td>Update to the 10th annual meeting of IRCH, Bonn, Germany, September 2017</td>
<td>11-13 September 2017</td>
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<td>Update to the 52nd session of the WHO ECSPP, Geneva, October 2017</td>
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1. INTRODUCTION

1.1 Background of guidelines development

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 evidenced by the global market which also experienced similar growth. Herbal medicines, including not only finished herbal products but also their starting materials for production, such as medicinal plants, herbal materials, and herbal preparations, are moving into the international commerce and the global trade arena, which indicates increased economic value and importance. When adverse events are reported to the regulatory authorities in relation to the use of herbal products, a large portion of them are attributable to poor quality of products, which may involve a variety of factors, including those due to natural (e.g. source material) and human (e.g. manufacturing/processing) factors. Hence, the safety and quality of herbal medicines at every stage of its production process, have become a major concern to health authorities, healthcare providers, the herbal industries and the public.

The safety and efficacy of herbal medicines largely depend on their quality. Unlike other pharmaceutical products, which are 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 drugs.

A number of World Health Assembly (WHA) resolutions relating to traditional medicine has requested WHO to provide technical support to develop methodology to monitor or ensure the quality, efficacy and safety of herbal medicines. The International Conferences of Drug Regulatory Authorities (ICDRAs), and annual meetings of International Regulatory Cooperation for Herbal Medicines (IRCH), 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.

Process and context

Participants of the WHO Informal Meeting on Methodologies for Quality Control of Finished Herbal Products (held in Ottawa, Canada, 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 where 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 other 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, since then, undertook the development of four new guidelines and to update other existing documents in order to provide technical guidance for 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 cover:

- WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants (published in 2003) [WHO, 2003a];
- WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (published in 2007) [WHO, 2007b];
- WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines (in press) [WHO, 2017]; and
- WHO guidelines on good herbal processing practices (GHPP) for herbal medicines (present document).

WHO has also updated two key technical guiding documents:

- WHO guidelines on good manufacturing practices (GMP) for herbal medicines (published in 2007) [WHO, 2007a]; and
- Quality control methods for herbal materials (published in 2011) [WHO, 2011], which includes the WHO good practices for pharmaceutical quality control laboratories as an annex.

GACP for medicinal plants are only the first step in quality assurance. The next important phase involves the GHPP of herbal materials. The processed materials are herbal materials or herbal preparations, which may be used as a starting source material for the GMP production of finished herbal products, or directly employed as herbal medicines in various herbal dosage forms. For this reason, GHPP for herbal medicines is integrally linked to GACP for medicinal plants and GMP for herbal medicines in the quality assurance and control of herbal medicines.

The present guidelines are intended to complement, and should be read in conjunction with, those guidelines provided in WHO guidelines on GACP for medicinal plants [WHO, 2003a] and WHO guidelines on GMP for herbal medicines [WHO, 2007b]. Altogether, the present guidelines plus the above-mentioned three new and two updated WHO guidelines form the core technical guidance for the overall quality assurance and control of herbal medicines.

Preparation of the guidelines
The original title suggested for these guidelines was “Good processing practices for herbal materials”. In November 2014, WHO convened the second WHO consultation on quality control of herbal medicines with financial support of Department of Health of Hong Kong
SAR, China, in Hong Kong SAR, during which the working draft guidelines were reviewed and discussed, and the objectives, scope and proposed contents were discussed and agreed. First draft guidelines were revised through global review process.

1.2 Scope

Processing refers to the unique procedures of preparing herbal materials, herbal preparations and herbal dosage forms for therapeutic applications. The process concerns ensuring the quality of the herbal materials, herbal preparations and herbal dosage forms produced. The safety and efficacy are strictly related to the intrinsic properties of the herbal materials.

These guidelines will provide technical guidance on good processing practices in the:

1. processing of herbs into herbal materials;
2. processing of herbal materials into herbal preparations; and
3. processing of herbal materials or herbal preparations into herbal dosage forms.

In the case of processing herbs into herbal materials, the “primary” process is involved; whereas in the case of processing of herbal materials into herbal preparations, “secondary” or “special” processes are involved. On the other hand, for processing herbal materials or herbal preparations into herbal dosage forms, the processing procedures involve the good practice of the preparation or GMP for the production.

An outline of the major processes and examples of procedures are given below.

1.2.1 Processing of herbs into herbal materials

Primary processing encompasses the immediate post-harvest treatments accorded to herbs obtained from cultivation or by wild crafting or field collection intended to free them from foreign matters, untargeted plant materials and other contaminants, and includes, for example, the procedures of sorting (garbling), washing, drying, cooling and freezing, where appropriate. Primary processing is applied to herbs in the preparation of herbal materials.

1.2.2 Processing of herbal materials into herbal preparations

Secondary processing is the next step concerned with converting the primary processed herbs (herbal materials) into herbal preparations by various additional procedures, including, for example, cutting, sectioning, comminution (fragmentation), aging/sweating; baking/roasting; boiling/steaming; and stir-frying.

Secondary processing may also involve special processing, an extension, in which a specialized method is employed to treat selected herbs with the view of reducing the contents of toxic ingredients or altering the chemical composition in order to modify their therapeutic activity. Examples of herbs so processed include Aconitum, nux-vomica and Panax species.

The herbal preparations described above may serve as crude materials for use as herbal medicines. In many cases, they will undergo further treatment procedures before being used
to manufacture the finished herbal products. The active ingredients are usually not purified
but rather are obtained along with other components of the medicinal plant part. Sometimes
the 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, purification, concentration, fermentation, or other chemical/biological methods.

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
products or as final dosage forms for therapeutic applications. In the latter case, it is not
uncommon that simple dosage forms are prepared from either herbal materials (such as
unprocessed seeds or plant exudates) or herbal preparations (such as ground powders and
dried extracts) ready for administration to the patients. These herbal dosage forms, produced
under GMP conditions, include liquid extracts, decoction, tea bags, granules, syrups,
ointments/creams, inhalations, patches, among others.

1.3 Objectives of guidelines

These new guidelines will provide technical guidance on good herbal processing practices
(GHPP) for the production of herbal materials, herbal preparations and finished herbal dosage
forms. 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 for the preparation of herbal materials from
herbs/herbal plant;
- provide technical information on good herbal processing techniques and procedures
applied for the production of herbal preparations from herbal materials;
- provide technical information on good herbal processing techniques and procedures
applied for the production of dosage forms of herbal medicines;
- provide a model for the formulation of national and/or regional good herbal processing
practice 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, and to promote safety, efficacy and sustainability of herbal
medicines.

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), for example:

- *WHO guidelines on good agricultural and collection practices (GACP) for medicinal
The WHO guidelines on good herbal processing practices (GHPP) 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 appropriate authority. The present document concerns the assurance of the quality of the herbal materials being prepared through various methods and steps of processing of the medicinal plant and its medicinal plant part obtained under GACP; and of the herbal preparations being prepared through various methods and steps of processing of the herbal materials. Herbal materials can be used directly as herbal medicines or to serve as source materials for the GMP production of finished products. These guidelines are applicable to the processing operations from post-harvest to finished herbal products. The processing of medicinal plants or plant parts should meet all applicable national and/or regional quality standards. The guidelines therefore may need to be adjusted according to local legislation and practice in each Member State. Each Member State should develop its own national guidelines on good herbal processing practices for herbal medicines that are appropriate to the country’s actual situation.

1.4 Definitions of terms

The terms used in these guidelines are defined below. The terms and their definitions have been selected and adapted from other WHO documents and guidelines that are widely used by WHO Member States, as well as from other reference sources (reference source is indicated with [ ]). These definitions may differ from those included in national regulations, and are therefore, for reference only.

1.4.1 Terms related 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 for patients. [WHO, 2017, in press]
Note: In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials). [WHO, 2017, in press]

**Herbs** [WHO, 2017, in press]
Herbs are crude plant material which may be entire, fragmented or powdered. Herbs include, e.g. the entire aerial part, leaves, flowers, fruits, seeds, roots, barks (stems) of trees, tubers, rhizomes or other plant parts.

**Herbal materials** [WHO, 2017, in press]
Herbal materials include, in addition to herbs, other crude plant materials. Examples of these other plant materials include gums, resins, balsams, exudates.

**Herbal preparations** [WHO, 2017, in press]
Herbal preparations are produced from herbal materials by physical or biological processes. These processes may be extraction (with water, alcohol, supercritical carbon dioxide (CO₂)), fractionation, purification, concentration, fermentation, and other processes. They also include processing herbal materials with a natural vehicle or steeping or heating them in alcoholic beverages and/or honey, or in other materials. The resulting herbal preparations include, among others, simply comminuted (fragmented) or powdered herbal materials as well as extracts, tinctures, fatty (fixed) or essential oils, expressed plant juices, decoctions, cold and hot infusions.

**Finished herbal products** [WHO, 2017, in press]
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 herbal products in the forms in which they are marketed for use or taken by the patient. They are produced either from herbal materials (such as dried roots or leaves) or herbal preparations (such as freeze-dried extracts). The herbal dosage forms may contain substances originated from a single herb or a combination of herbs.

**Medicinal plants** are plants (wild or cultivated) used for medicinal purposes [WHO, 2003a]; [WHO, 2007a].

**Medicinal plant materials:** see Herbal materials
1.4.2 Terms related to herbal processing practices

Processing
The processing of herbal materials refers to a series of post-harvest treatments applied to the crude medicinal plant materials. For the purpose of the present guidelines, “processing” includes primary processing, such as sorting, removal of untargeted plant materials, cleaning, and drying as described in the WHO guidelines on GACP for medicinal plants [WHO, 2003a]; it also includes secondary and special processing as defined in the present guidelines.

Primary processing
Primary processing refers to a series of simple preparatory procedures that may be performed at the harvest/collection site, including sorting, removal of untargeted plant materials, cleaning, drying, and where appropriate, cooling and freezing.

Secondary processing
Secondary processing refers to the preparative steps applied to herbs in addition to the primary processing before they can be used as materials for therapeutic treatment or as intermediate materials for manufacturing of finished herbal products. They are considered important pharmaceutical techniques in the herbal industry, through which purity of raw herbs is assured (such as removal of foreign matter, prevention of microbial and insect infection/infestation), and the therapeutic properties of raw herbs are altered (such as enhancement of effectiveness or reduction of toxicity). The secondary processing procedures may vary from one herbal material to another, depending on the characteristics of the active ingredients as well as the therapeutic purposes. These processes, along with below described “Special Processing”, have been grouped under the term “specific processing” in the WHO guidelines on GACP for medicinal plants [WHO, 2003a].

Special processing
Special processing is an extension of the secondary processing by further treatments using a series of well-defined special procedures after the general secondary processing, for the purpose of further detoxification of some toxic herbs (e.g. aconite) or further enhancement of the therapeutic properties (e.g. ginseng). It is often practiced by the herbal industry according to traditional medicine knowledge and customs.

Adjuvants
Adjuvants are adjunctive substances used during the herbal processing procedures alongside the herbal materials, included for the purpose of altering the pharmacological/therapeutic properties of the herbal preparations or neutralizing/reducing toxicity. Common adjuvants include wine, vinegar, honey, milk, and clarified butter, among other materials.

1.4.3 Terms relating to quality control

For a comprehensive list of terms on quality control of herbal medicines, please refer to the WHO guidelines on GMP for herbal medicines [WHO, 2007a], Good Manufacturing Practices for pharmaceutical products: main principles [WHO, 2014]; Quality control...
methods for herbal materials [WHO, 2011], and WHO guidelines for selection of substances of herbal origin for quality control of herbal medicines [WHO, 2017]. The following terms are more directly or indirectly applicable to the present guidelines than others.


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)** [WHO, 2007a – WHO, 2003b]; [WHO, 2014]

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.


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.


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

**Good manufacturing practice (GMP)** [WHO, 2014]

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.


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


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.
Chemical reference substance (or standard) [WHO, 2007c]
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.

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.

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

2. GOOD HERBAL PROCESSING PRACTICES FOR THE PRODUCTION OF HERBAL MATERIALS

2.1 General information
Processing for the preparation of herbal materials from medicinal plants is often specific to the medicinal plant and to the part and may involve unique procedures. The particular processing methods may have a history as old as the use of medicinal plants, and they are sometimes proprietary procedures. Many of the traditional processing procedures are subject to standardization in modern settings.

When the medicinal plant and its parts are obtained through wild collection or cultivation under GACP for medicinal plants [WHO, 2003a], they must be subjected to a series of good practice of post-harvest processing procedures. The exact processing procedures may vary from one herbal material to another. Some consist of only a few simple steps such as sorting, cleaning and drying, and they are generally referred to as the “primary processing”. Others may require some more complicated steps such as cutting, sectioning, comminuting, aging/sweating, baking/roasting, boiling/steaming, and stir-frying, for the purpose of improving the purity, preventing damage from mould and other microorganisms, detoxifying intrinsic toxic ingredients, or enhancing therapeutic efficacy. Such processing procedures are referred to as the “secondary processing” in these guidelines. They may have a significant impact on the quality of the resulting herbal preparations.

Special processing is an extension of the secondary processing by further treatments using a series of well-defined special treatment procedures applied to the herbs for specific purposes such as reduction of toxicity or alteration/modification of therapeutic properties. Examples of herbs (medicinal plants) using special processing include Aconitum, nux-vomica and Panax species.

The safety and efficacy of herbal medicines are closely dependent on the quality of the
starting and processed source materials. To assure their quality, the good practices for processing herbal materials may be considered. In general, good practices for processing herbal materials mirror the good manufacturing practices for herbal medicine as delineated in the *WHO guidelines on GMP for herbal medicines* [WHO, 2007a], with the first step being the post-harvest handling and preparation of the starting medicinal plant materials under sanitary conditions. All critical equipment for processing must be qualified; all processing methods and procedures are standardized (SOP); master formulae, master and batch records documented; and quality control parameters established and adhered to. GHPP monograph/SOP protocol on specific herbal material should be developed and implemented.

### 2.2 Purposes and functions of processing

Through experiences gained over the centuries, knowledge has been acquired for the development of processing procedures for maximizing the quality and therapeutic value of herbal materials. The final form of a herbal medicine depends upon the nature of the herb and its intended use. In general, the traditional processing of herbal materials serves several purposes, such as concentrating the components, removing undesirable substances, modifying the therapeutic properties, facilitating dispensing and compounding, and facilitating storage. Thus, the major objectives for the processing of herbal materials are summarized as below.

#### Neutralization of toxicity and diminishing side effects

Herbal materials that possess significant levels of toxicity, highly potent pharmacological activity or being known to cause severe side effects must be pre-treated in certain 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 medicinal plants that are known to contain toxic or undesirable chemical components; they must be properly processed to remove those unwanted substances. Through the pre-treatment processes such as “steaming” and “frying”, the heat-sensitive toxic components will be degraded. In other cases, processes such as “sweating” and “aging” would result in enzymatic degradation of the toxic ingredients. For example, raw aconite (*Aconitum* species) root, containing significant amounts of toxic alkaloids such asaconitine, must be boiled or steamed for hours to hydrolyse aconitine into less toxic derivatives. In the case of cascara (*Frangula purshiana*, synonym *Rhamnus purshiana*) bark, they have to be aged for at least one year before use, to allow oxidation to occur, by which the strongly laxative hydroxyanthracene glycosides are converted to oxidized compounds of lower laxative potencies.

#### Modification of therapeutic properties

Some herbal materials require specific processing to alter their therapeutic properties. For example, rhubarb (*Rheum palmatum*) 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 action of some herbal materials may be changed through processing. For example, the unprocessed raw rehmanna (*Rehmannia glutinosa*) root is used to treat fever, hypertension and skin eruptions; whereas after being cooked in wine, the processed
rehmannia is often used for tonic and anti-aging purposes in some traditional medicine context.

In the case of ginseng (*Panax ginseng*) roots, different post-harvest processing procedures give rise to several processed products, such as "white ginseng" and "red ginseng". "White ginseng" is the material dried by the sun or heat, whereas "red ginseng" is prepared through a series of steaming and cooking steps. These two types of ginseng products have found different uses in some traditional medicine context, the former can nourish the Yin function while the latter supports Yang.

**Enhancing efficacy and reinforcing therapeutic effects**

The therapeutic efficacy of certain herbal materials can be augmented through specific methods of preparation. For instance, the pain-relieving property of corydalis (*Corydalis yanhusuo*) rhizomes is believed to increase when they are stir-fried with rice vinegar. Similarly the honey-treated ephedra (*Ephedra* species) is regarded to possess stronger antitussive and anti-asthma properties than the unprocessed ephedra, which is mostly used as a diaphoretic.

### 2.3 Processing techniques and procedures

Appropriate measures of general processing are dependent on the individual materials. These processes should be carried out in conformity with state/provincial, national and/or regional quality standards, regulations and norms. These protocols should also comply with the regulatory requirements that apply in the producer and the purchaser countries. The SOP of processing should describe in detail the various operations to be performed on the medicinal plant material, such as sorting, washing, drying, crushing, milling, pulverization and sifting. They should also include the length of time and temperature, among others. As much as possible, the SOP should be followed. If modifications are made, they should be justified by adequate test data demonstrating that the quality of the herbal materials is enhanced and/or not compromised.

#### 2.3.1 Preparation of harvested/collection medicinal plant part for processing

Harvested or collected raw medicinal plant materials should be promptly unpacked upon arrival at the processing facility. Prior to processing, they should be protected from rain, excessive sunlight, moisture and any other conditions that might cause microbial growth, mould, aflatoxin formation, fermentation and thermal degradation. The unprocessed raw medicinal plant materials should be stored in appropriate containers under adequate and ventilated environmental conditions (special conditions of humidity and temperature may be required and monitored); as well as protected from insects, rodents, birds, livestock, domestic animals, and other pests.

Consistent quality for the finished herbal products can only be assured if the starting raw medicinal plant materials are defined in a rigorous and detailed manner. For this reason, the crude/raw medicinal plant materials must be adequately documented prior to the secondary processing procedures to include, as far as possible, the following information;
• Botanical name (Binomial), synonyms, and applicable variety, local name; plant part(s) of the medicinal plant;
• Source (cultivation/wild growing region);
• Accession number/information;
• Name and affiliation of collector or supplier;
• Batch (or lot) number and size;
• Collection (harvest) conditions (e.g. season/month and date; plant part; wet/dry environment);
• State of the plant material (e.g. fresh or dried);
• Botanical authentication of the source medicinal plant materials;
• Physical appearance such as colour, odour, form, shape, size and texture;
• Suitable identification tests such as thin-layer chromatography (TLC) or other chromatographic fingerprints;
• Assay results, where appropriate, of active ingredient(s) or chemical reference standard(s);
• Limit tests such as ash value, water content, and extractives; and
• Determination of possible contaminants such as pesticides and heavy metals, mycotoxins, microbiological load, and where appropriate, fumigation sulphur residue, and radioactivity.

2.3.2 Primary processing procedures

Harvested/collected medicinal plants and/or their parts undergo a series of post-harvest (and post-collection) good practice of processing procedures, which in the broadest sense include all steps from the immediate on-site primary clean-up of the desired medicinal plant part to its being processed into a form (herbal materials) ready for therapeutic use or as a starting source material for the production of a finished herbal products. While the exact processing methods may differ from one herbal material to another, the procedures shall be adopted from those good practice protocols specified in the national pharmacopoeia or recommended by other authoritative documents of the end-user’s country. In the event that no acceptable good processing procedures are available, or that modification of existing or reference cited protocols are required, they should be justified by adequate quality control test data that the quality of the herbal material is not diminished. In the absence of national/regional procedures or protocols, international guidelines, such as WHO guidelines on GACP for medicinal plants [WHO, 2003a], and the present guidelines, may be consulted.

2.3.2.1 Sorting (Garbling)

The sorting process serves as the first step to ensure the purity and cleanliness of the medicinal plant materials. After the bulk amount of the desired plant part is harvested or collected, all extraneous and unwanted matters including dirt (e.g. soil, dust, mud, stones), impurities (e.g. insects, rotten tissues, untargeted medicinal plants and/or plant parts), and residual non-medicinal parts must be separated from the medicinal part(s). The process may involve, depending on the plant material, procedures such as removing dirt and foreign substances, discarding damaged parts, peeling (to separate unwanted plant parts from the medicinal plant parts 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 residuals of unwanted plant parts (e.g. removing unwanted seeds from fruits and stripping leaves from...
stems). Although sorting may be done by mechanical means in some cases, it is usually performed by hand operation. Only suitably trained and equipped (e.g. gloves, dust mask, etc. as appropriate) staff should carry out this work.

2.3.2.2 Washing

Raw medicinal plant materials, especially roots, rhizomes and tubers, are usually washed with clean water, dried soon after harvest/collection. During the washing process, scraping and brushing may be necessary. It is generally recommended not to soak the medicinal plant materials in water for an unnecessarily long period of time. Change water frequently as required.

2.3.2.3 Parboiling (Blanching)

After washing, certain raw medicinal plant materials may undergo a parboiling or blanching process in which they are put into boiling water for a brief period of time 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 and preventing mould/insect contamination, and facilitating further processing such as removal of the seed coat of almonds.

2.3.2.4 Leaching

Some impurities can be removed by the action of running water over the raw medicinal plant materials. The length of leaching has to be controlled in order to prevent excessive loss of other ingredients.

2.3.2.5 Drying

Unless used in the fresh state, the raw medicinal plant materials are to be dried after being sorted and washed. In general, they must be dried as soon as possible in order to reduce damage from mould and other microbial infestation. Drying will also avoid tissue deterioration and phytochemical alteration caused by the actions of enzymes and microbial organisms; and will also facilitate grinding and milling, and convert the herbal materials into a convenient form for further processing.

The final moisture content for dried herbal materials varies depending on the tissue structure, but should generally be below 10-12%. Information on the appropriate moisture content for particular herbal material may be available from pharmacopoeias or other authoritative monographs.

Proper drying involves three major aspects: control of temperature, humidity and air flow. 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 proper operational procedure is crucial. Information on the appropriate drying methods and procedures for particular herbal materials may be available from pharmacopoeias or other authoritative monographs. In general, raw medicinal plant 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 medicinal plant material. They are dependent on the characteristic (e.g. volatility, stability) of the ingredients and the texture of the plant part collected (e.g. root, leaf or flower). In general, the following drying processes can be adapted.

**Sun-drying**

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

In the case of natural drying in the open air, medicinal plant materials should be spread out in thin layers on drying frames and kept away from possible contaminations such as vehicle exhaust, heavy dusts, and rain, as well as 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 be located at least 15 cm above the ground. Efforts should be made to achieve uniform drying within the shortest period of time to avoid mould formation.

**Shade-drying**

Some medicinal plant materials can be dried in the shade with or without artificial air flow to avoid direct exposure to strong sunlight. The drying process is slow, but it is preferred 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 more rapid than open-air drying and is often necessary on rainy days or in regions where the humidity is high. Medicinal plant materials may be dried by means of ovens, stoves, rack dryer, tunnel dryer, belt driers, other heating devices or with open fires. The use of open fire should be avoided as much as possible, as residues of combustion may introduced contamination. When 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 drug 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 ingredients. In general, the temperature should be kept below 65°C for barks and root and below 40°C for leaves, herbs and flowers.

**2.3.3 Secondary processing procedures**

In addition to the primary processing, the *WHO guidelines on GACP for medicinal plants* [WHO, 2003a] also addressed, albeit very briefly, the fact that some herbal materials require “specific” processing to improve their purity and quality. In the current guidelines, this term is delineated into “secondary” and “special” processing. This section highlights the principles and practice of the commonly used secondary processing techniques. In all cases, good in-
process control measures must be employed to assure the quality of the end product. National and/or regional botanical and chemical quality standards for each processed herbal material must be met. In absence of national standards, regional or international pharmacopoeial standards may be adopted. Guidance for compliance measures can be found in the annex to the Quality control methods for herbal materials [WHO, 2011], WHO guidelines for selection of substances of herbal origin for quality control of herbal medicines [WHO, 2017], WHO guidelines on GMP for herbal medicines [WHO, 2007a], and the present guidelines. An example of a model format of good herbal processing practices monograph/SOP protocol on secondary processing is given as Annex 1.

The applicable procedures of the secondary processing nature are as follows:

2.3.3.1 Cutting, sectioning, and comminution (see also section 3.2.1.2 for Comminution (fragmentation)/grinding/milling)

When thoroughly dried, the herbal materials are processed by cutting and sectioning into convenient or specific sizes and shapes or forms for storage or direct use as decoction slices/pieces, and/or further processing for the manufacture of herbal preparations or finished herbal products. 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/pulverized into powder form according to common practice found in herbal medicines for use as a finished herbal products.

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

2.3.3.2 Aging/Sweating

The aging (or wilting) process refers to storing the herbal materials for a period of time after being harvested or collected from the field prior to use. It is generally done under the sun or in the shade for up to a year, depending on the specific herbal material. During the process of aging, excessive water is evaporated and enzymatic reactions (such as hydrolysis of the glycone portion from glycosides) may occur to alter the chemical composition of the herbal material. For example, cascara (Frangula purshiana, synonym Rhamnus purshiana) bark should be aged for at least one year (or artificially heated to speed up the process) prior to use in medicinal preparations, for the purpose of curtailing the strong irritating effects that may cause vomiting and upset stomach.

A similar process known as sweating involves keeping the herbal materials at a temperature of 45-65 °C with high humidity for an extended period of time, from one week to a couple of months, depending on the plant species. The herbal materials are usually densely stacked between woollen blankets or other kinds of cloth. 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.

For example, vanilla beans (Vanilla planifolia) are well known to undergo repeated sweating
between woollen blankets in the sun during the day and packing in wool-covered boxes at night for about two months, during which the vanilla pods lose up to 80% of weight and take on the characteristic colour and odour of the commercial drug.

2.3.3.3 Baking/Roasting
The baking/roasting process is a dry-heating using indirect, diffused heat, where the herbal materials are put in a heating device, often embedded in bran or magnesium silicate (talc) powder to ensure even heating on 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/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, the processing procedure of nutmeg (*Myristica fragrans*) and kudzu (*Pueraria montana var. lobata*) root requires being roasted with bran.

2.3.3.4 Boiling/Steaming
The boiling process involves cooking the raw medicinal plant materials in water or another liquid solvent such as vinegar, wine, milk or other vehicles.

In the steaming process, raw medicinal plant materials and/or herbal materials are kept separate from the boiling water but have direct contact with the steam, resulting in a moist texture to the herbal materials. Such treatment is often done by placing the herbal materials in a steamer or in a special utensil equipped with a flat frame hanging 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/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* (synonym *Polygonum multiflorum*) root is often steamed in the presence of a black-bean decoction in order to enhance its tonic effects. Boiling the raw medicinal plant materials such as *Croton tiglium*, *Abrus precatorius*, *Nerium oleander* (synonym *N. indicum*), and *Gloriosa superba*, in cow’s milk is practiced in some traditional medicine context to reduce the levels of their toxic ingredients and thus diminish the toxicity of the herbal materials.

2.3.3.5 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 medicinal plant species, the stir-drying 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 on 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) root and rhizome and Astragalus mongholicus (synonym A. membranaceus) roots are often stir-fried with honey for the preparation of decoction slices, whereas the Salvia miltiorrhiza root is stir-fried with wine. In the case of ginger, fresh ginger is often stir-fried together 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.

2.3.3.6 Fumigation
Fumigation by sulphur dioxide has been employed in post-harvest handling of some medicinal herbs for the purpose of preserving colour, improving fresh-looking appearance, bleaching, preventing the growth of insect and overcoming decays 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 much 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 (e.g. limits on sulphur residue) should be complied with.

2.3.3.7 Irradiation
In some cases, infrared or ultraviolet lights can be used to eliminate or reduce microbial load of the medicinal plant materials. The use of these procedures has to comply with the national and/or regional regulations.

2.3.3.8 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 for the same medicinal plant/plant part, 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, consult the national or regional regulatory standards and other literature sources to decide on the most appropriate method to use. Once a method is adopted, adhere to the SOP 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 both the grower/collector, manufacturer and the end-user countries.

2.3.3.9 Temperature
With in-processing procedures that involve heating, the temperature used is critical. Ensure that the required temperature is achieved during the process. In some cases, pre-heating the equipment (e.g. 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 (e.g. electric oven) is used, the heating device should be regularly calibrated.

2.3.3.10 Duration of procedure/treatment

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

2.3.3.11 Use of adjuvants

Any adjuvant (e.g. wine, vinegar, salt, ginger juice and honey) used in the processing procedures should be of the required/appropriate quality. The quality of adjuvants must be clearly defined and controlled (according to pharmacopoeial requirements 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.

2.3.4 Special processing procedures

For herbal materials derived from toxic medicinal plants, general primary and/or secondary processing might be insufficient to reduce or attenuate their adverse effects. Such herbal materials require further special processing procedures before they can be used for therapeutic purpose. These special processing procedures serve as a means to detoxify or neutralize the toxicity, or to reduce the side effects. Such processes are particularly important for those medicinal plant parts that are known to contain toxic or undesirable chemical components; they must undergo proper processes in order to have the unwanted substances degraded. On the other hand, a number of herbal materials require special methods of processing in order to enhance their therapeutic efficacy or to modify their therapeutic properties for the treatment of other disease conditions. The following are examples of special herbal material processing used in some traditional medicine context.

2.3.4.1 Detoxification

- Aconite (Aconitum species) root is a highly toxic substance and should not be taken in the crude form. Only after proper processing procedures can the toxicity of aconite root be reduced so that it becomes suitable for use in herbal medicine by trained practitioners. The specific process generally involves boiling in water or steaming, or both, to significantly reduce the content of aconitine and related alkaloids.
- Nux-vomica (Strychnos nux-vomica) seeds are specifically processed by frying in ghee/clarified butter or boiling in water or other media such as cow’s milk to reduce the content of their toxic ingredients, strychnine and brucine.
- Pinellia ternata tuber: To reduce the gastrointestinal irritant property, the raw herb is soaked in a solution containing glycyrrhiza and calcium oxide at a pH ≥ 12. Another way of reducing the irritant property is soaking in water together with potassium aluminum
sulphate, or boiled in water together with ginger and potassium aluminum sulphate.

- **Arisaema erubescens** rhizome: The raw medicinal plant material is first soaked in water together with potassium aluminum sulphate for several days, followed by cooking with ginger and potassium aluminum sulphate to reduce the strong irritant effect on the respiratory and gastrointestinal tracts. An alternate method for processing Arisaema rhizome is by steaming with animal bile.

- **Euphorbia kansui** and **E. pekinensis** herb: Processing by frying with vinegar is needed to degrade the toxic components that cause severe vomiting and diarrhoea, and central nervous system poisoning.

- **Seeds of Xanthium strumarium** (synonym X. sibiricum), **Ricinus communis** and **Croton tiglium** are often processed by stir-frying for the purpose of degrading their contained toxic proteins.

- **Cascara sagrada** (*Frangula purshiana*, synonym *Rhamnus purshiana*) bark: Following primary post-harvest processing, the bark is aged (stored) for at least one year prior to use as a laxative. During the aging period, natural enzymatic action reduces the drastic cathartic potency of its active glycoside constituents to a non-toxic level.

### 2.3.4.2 Modification of therapeutic properties

- **Ginseng** (*Panax ginseng* and *Panax quinquefolius*): Fresh ginseng is converted to red ginseng through a series of repeated steaming procedures to afford a product with altered medicinal properties.

- **Corydalis yanhusuo** rhizomes are stir-fried or cooked with rice vinegar to enhance their analgesic property.

- **Rehmannia glutinosa** root: The unprocessed herbal material is used to treat fever, hypertension and skin eruptions; whereas after being cooked in wine, the processed rehmannia is used as a tonic and anti-aging drug in some traditional medicine context.

### 2.3.4.3 Use of adjuvants

Common adjuvants used during the special processing procedures include wine (e.g. rice wine, wheat wine, and sorghum wine), vinegar, honey, ginger juice, liquorice extract, cow milk, ghee and brine, etc. Under special circumstances, other auxiliaries such as, other animal derived materials including their tissues and secretions (e.g. goat milk, animal bile, goat fat, cow’s urine), butter, black bean extract, coconut water, tamarind juice, turmeric, lemon juice and mineral materials (e.g. borax) have been used. The quality of adjuvants must be clearly defined and controlled (according to pharmacopoeial requirements and/or relevant regulatory requirements).

In addition, the use of any materials derived from animal/animal products in any processing procedures should be evaluated for safety and contamination, especially of pathogens, prior to use. General guidance could be found e.g. in *Safety issues in the preparation of homeopathic medicines* [WHO, 2010].

### 2.3.5 Documentation

All processing procedures that could affect quality and safety of herbal materials should be documented. Guidance for good documentation can be found in the *Good Manufacturing
Practices for Pharmaceutical Products: main principle [WHO, 2007a; WHO, 2003b]; [WHO, 2014], as well as WHO guidelines on good agricultural and collection practices for medicinal plants [WHO, 2003a]. 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:

- Botanical (scientific) and the local/common names of the source medicinal plant material; and plant part(s) being processed;
- Site and time of harvesting/collection;
- Batch number and any other identification code;
- State of the plant (e.g. fresh or dried);
- Dates of receipt of the material, processing of the material, and completion of the process;
- Name of person in charge of the processing;
- General processes that the plant material has already undergone (drying, washing, cutting, for example., 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, amount and quality grade of the auxiliary (e.g. wine, vinegar) and/or other substances (e.g. sand, bran) used, temperature control, length of processing time, after-process steps (e.g. cooling, drying, cutting), and other relevant information;
- Batch production detail deviations/modifications of the master formula;
- In-process control, e.g. organoleptic changes of the plant material after processing (such as change in colour, shape, texture, odour and taste);
- Quality control parameters, specifications, and assay results, where appropriate, of active ingredient(s) or Chemical reference standard(s); and
- Shelf-life/retest period.

3. GOOD HERBAL PROCESSING PRACTICES FOR THE PRODUCTION OF HERBAL PREPARATION

3.1 General information

The herbal materials described in Section 2 of these guideline 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 in many other cases, 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, purification, concentration, fermentation, or other chemical/biological methods. These include extracts, decoctions, tinctures, essential oils, and
3.1.1 Preparation of herbal materials for processing

- Authentication of herbal materials should be performed prior to extraction. Purity (devoid of contaminants) should also be ensured.
- Proper documentation on the herbal material should be available as recommended in Section 2.3.5.
- 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.
- All operational steps should be reproducible and performed hygienically, forming parts of the processing SOP.

3.2 Processing techniques and procedures

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 of good herbal processing practice monograph/SOP protocol to produce a herbal preparation is given as Annex 2. The general guidance is provided below.

3.2.1 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 medicinal plant matrix is to eliminate unwanted materials and to concentrate other constituents in a soluble form. Herbal extracts include decoctions, liquid extracts, soft extract, fluidextracts, tinctures, oleoresins, dry extracts, and others. The herbal preparations so obtained may be ready for use as a medicinal agent, or it may be further processed into finished herbal products such as tablets and capsules.

Various techniques are used for extraction, including maceration, infusion, digestion, percolation, and decoction. Modern separation techniques can also be applied, e.g. counter-current extraction, microwave-assisted extraction, ultrasonic extraction (sonication), and supercritical fluid extraction.

3.2.1.1 Common methods of extraction

In order to produce herbal preparations of defined quality, the use of appropriate extraction technology, extraction solvents, and type of equipment are crucial. Some common methods of extraction are illustrated 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 (in most cases at room temperature) for a defined period of time with frequent agitation. During the maceration process, chemical constituents are separated from the plant tissues through a dissolution process into the liquid solvent. A common practice is to put the herbal material in a container and add solvent until the herbal powder is thoroughly moistened. An additional amount of solvent is then introduced. The mixture is agitated at regular intervals for a defined period of time, strained, and the marc (the solid materials) is pressed. All liquids are collected, combined, and separated by decantation, centrifugation, straining or filtration. The maceration process may be repeated if desirable. 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 and solvent), and a definite duration should be specified. Exhaustive bulk extractions can be quite time-consuming and require large volumes of solvent.

In a special case, 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 microwave is 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 breakdown 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 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-scaled extraction; they are used mostly for the initial extraction of a small amount of material.

Infusion

Infusion refers to an extraction procedure in which the herbal material is immersed in hot liquid for a brief period of time to produce a dilute liquid preparation. Typically, the herbal material is steeped in hot water and allowed to stand for some time (15-20 minutes). Sometimes another part 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 ends). 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 plant powder for a day or two. 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 materials. 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 is pressed and all liquids are pooled to obtain the percolate. In addition to the solvent used for the extraction, the flow rate and the temperature would 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.

Decoction

Decoction is the most common method to make herbal preparations in various traditional medicine context. It involves boiling the herbal material in water, during which time the chemical ingredients are dissolved into the hot liquid. This procedure is suitable for extracting water-soluble and heat-stable ingredients of the medicinal plant and/or herbal materials.

A special technique of decoction is the “hot continuous (Soxhlet) extraction” using the Soxhlet apparatus. Typically, the Soxhlet instrument includes an extraction chamber with reflux condenser and a collection flask. The chamber is placed between the collection flasks and the condenser. The herbal powder or pieces are kept inside the extraction chamber. A suitable solvent is added to the flask and heated under refluxing. The solvent will first be evaporated up into the condenser, then liquefied and drops into the chamber and covers up the herbal powder. When the condensed solvent in the chamber reaches a certain height, it is siphoned back into the flask, and the next cycle of extraction starts. Usually, 50-60 times of recycling are necessary for an extraction to complete. Due to continuous extraction, this method is more efficient than simple decoction with less consumption of 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.

Supercritical fluid extraction

Supercritical fluid extraction is a modern technique making use of the solvating property of a supercritical fluid (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 (e.g. ethanol) to change the polarity of the supercritical fluid.

3.2.1.2 Steps involved in the extraction of herbs and herbal materials

The following steps are generally involved in the extraction procedures.

Comminution (fragmentation)/grinding/milling (see also section 2.3.3.1)
Prior to extraction, the medicinal plant part is generally dried and reduced to a size of 30-40 mesh (the actual size can be adjusted as the need arises). If fresh material is used for extraction, it is necessary to perform extraction as soon as possible after the material is collected to avoid deterioration (microbial fermentation). The purpose of powdering the plant 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 the air, and an excessively fine powder will block the pores of the extraction filter, slowing or preventing the passage of the filtrate.

**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 desirable chemical components, water or other solvents can be used, either at room temperature ("cold" extraction) or at an elevated temperature ("hot" extraction).

**Filtration**

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 filtering devices/methods, including decantation, centrifugation, or straining, may be used depending on the method of extraction and 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.

3.2.1.3 Common herbal preparations prepared by extraction

**Decoction**

A water-based herbal preparation made by boiling herbal materials with water, and is most common utilized in various traditional medicine context. Generally, it is recommended that only freshly prepared decoctions should be used. 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 materials and water used, as well as the length of the decocting process, should be specified.

**Infusion**

A dilute solution prepared by steeping the herbal materials in hot (sub-boiling) water over a short period of time. Infusions prepared in edible oil or vinegar are also available.

**Extract**

A preparation of liquid, semi-solid or solid consistency obtained from herbal materials by an extraction process using suitable solvents. “Liquid (fluid) Extract” is a liquid preparation of
herbal materials obtained using water, alcohol or other extraction solvents. When the evaporation of the solvent leads to a semi-solid extract composed of a resin in solution of an essential and/or fatty oil, it is called “Oleoresin”. In some cases, the solvent is partially evaporated to afford a semi-solid preparation called “Soft Extract”. When the solvent is completely removed, “Dry Extract” is obtained as a solid preparation. 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 multi-particulate granules.

Fluidextract
An aqueous alcoholic preparation typically made in a ratio of one part (e.g. one millilitre) of liquid to one part (one gram) of the extract of the original herbal materials.

Tincture
An ethanol extract of herbal materials, typically made up of 1 part of herbal material and 5-10 parts of solvent. Tinctures can be prepared by extracting herbal materials with ethanol of a suitable concentration or a spirit (an alcoholic beverage). The ratio of water to alcohol should be recorded.

Macerate
A liquid preparation extemporaneously 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.

3.2.1.4 Factors influencing extraction of herbal materials
There are a number of factors that would influence the efficiency and reproducibility of the extraction process. A few issues to consider include the solvent used to make an extract, particle size of the herbal material, the herb-to-solvent ratio, kind of extraction process (e.g. percolation or maceration), extraction time, temperature and other relevant conditions. All these factors should be optimized and incorporated into the SOP, and be strictly adhered to.

3.2.1.5 Selection of extraction methods
- The choice of extraction method is governed by the nature (stability, solubility, etc.) and amount of material to be extracted. For large amounts, the feasibility of extracting in bulk scale should be considered.
- The extraction method should be as exhaustive as possible, i.e. removing as much of the desired ingredients as possible from the plant matrix.
- It should be fast, simple, economical, environment-friendly, and reproducible.

3.2.1.6 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 for use. While water has been, and is, most commonly used as a solvent, organic solvents of varying polarities are generally selected in modern methods of extraction to exploit the various solubilities of plant constituents. For example, an aqueous solution of alcohol (e.g. 60-80% aqueous
ethanol) can extract the majority of organic secondary metabolites from herbal materials. Other solvents may apply for the extraction of specific types of ingredients (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 material safety data sheet (MSDS) should be reviewed and appropriate protective measures should be used. Precautions must be taken to minimize the risk of fire and explosion. Care should be taken to reduce environmental contamination and to protect the workers and other people in the vicinity from exposure to chemical hazards.
- Toxic solvents and those detrimental to the environment, e.g. benzene, toluene, and carbon tetrachloride, must not be used. Diethyl ether should 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 by ICH (CPMP/ICH 238/95), according to their potential risk, into:
  - 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) [WHO, 2007b].
- Solvents of general-purpose grade available in plastic containers are often contaminated by plasticizers, and minimizing contamination is especially important when bulk extraction is carried out 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 away from direct exposure to sun light.
- When solvents are recycled, strength and purity must be confirmed prior to re-use. Recycled solvent should be used in the same extraction process only.
- Waste solvents must be disposed safely and properly. Guidelines from national, local, or institutional regulations of waste solvent disposal must be strictly observed and followed.
- Limits for solvent residue may be 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 under 40 °C, unless evidence is available for the use of higher temperatures.
- For heat stable constituents, Soxhlet extraction or decocting in boiling water 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 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 ingredients.

- The number of repeated extraction cycles required for the complete removal of the desirable constituents is as important as the length of time per each extraction.
- The length of extraction time and the number of cycles should be controlled and recorded.

### 3.2.2 Distillation

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

Water or steam distillation is a method of choice for extracting volatile ingredients from medicinal plants. In brief, the herbal material is packed in a still, a sufficient amount of water is added and brought to a boil (water distillation). Alternatively, a stream of steam is introduced to the herbal material pre-soaked in water (water-steam distillation), or a stream of steam is introduced to medicinal plant 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 plant materials to avoid steam to penetrate into the materials such as rose flowers, while direct steam distillation is often used for fresh or dried medicinal plant materials. Freed from the plant tissue, the essential oil is carried away with the steam. Upon condensation, both water and oil are collected in the liquid form, and the latter separates from the former into two immiscible layers.

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

For volatile oils that may be decomposed during distillation, they can be obtained by expression (mechanical pressing), solvent extraction, supercritical carbon dioxide extraction, or by the enfleurage process for delicate flowers of which volatile chemicals may decompose during distillation.

### 3.2.2.1 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, e.g. heating rate and distilling rate, have to be specified and controlled.
- The equipment employed should be in conformance with the official safety standards and all procedures must conform to the operational instructions and safety requirements.
- The water used for distillation should at least comply with local requirements for drinking water.
3.2.3 Fractionation and Purification

Fractionation is a separation process in which a mixture is divided into a number of smaller quantities (fractions) with higher content of target substances (compounds). The crude extracts of herbal materials contain complex mixtures of secondary metabolites with diversified chemical and physical characteristics. It is often desirable to divide the chemical constituents into different groups based on their similarities in chemical and physical properties, such as a flavonoid-rich preparation, total glycosides, or an alkaloid fraction. Fractional separation of an 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 semi-purified preparations in order to enrich active constituents, to remove inactive and/or toxic constituents.

3.2.3.1 Liquid-liquid partition

The liquid-liquid partition (or solvent partition) method involves the use of a series of liquid solvents. The herbal extract is usually dissolved or suspended in water and partitioned with organic solvents successively in a sequence of increasing polarities, e.g. n-hexane, dichloromethane, ethyl acetate, and water-saturated n-butanol. As a result, chemical compounds possessing different polarities are transferred from the water portion to different solvent fractions according to the principle of “like dissolves like”. For example, the initial step of partition using non-polar solvents (such as n-hexane or petroleum ethers) removes lipophilic substances (such as alkanes, fatty acids, sterols) from the herbal mixture, and such a process is sometimes referred to as “defatting”. The compounds with intermediate polarity (such as flavonoids and quinones) will dissolve in the medium-polarity solvents (such as dichloromethane and ethyl acetate), whereas more polar compounds (such as glycosides, polyphenols) will be concentrated in the more polar solvents (such as butanol) or retained in the water phase.

The counter-current extraction technique can be applied for fractionation and purification purposes, where applicable.

3.2.3.2 Chromatography

Further purification of the extract fractions can be achieved by various chromatographic techniques, of which column chromatography is 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 (sorbents) 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 constituents in the herbal extract.

3.2.3.3 Fractionation and purification procedures

Liquid-liquid partition

- The storage, use, and disposal of solvents must be handled with care and in conformance with the national/local/institutional regulations.
The experimental procedures should be carried out in certified facilities with sufficient ventilation and safety measures. They are preferably performed inside fume hoods.

**Column 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 (e.g. 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.

### 3.2.4 Concentration and drying

The herbal extracts or semi-purified extracts are often concentrated to produce a concentrated liquid preparation by the removal of excessive 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 or mixture of solvents are not reusable. The degree of 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 compounds may be subject to degradation. The liquid preparation so obtained may be used as is or further processed into a dry extract.

When complete drying is required, the drying process can make use of vacuum freeze dryers, cabinet vacuum dryers, continuously operating drum or belt dryers, microwave ovens, or atomizers. The technique for drying depends on the stability of the product and the amount of moisture that must be removed. The total removal of solvent results in a dry extract, which is less subject to microbial contamination than are liquid extracts. Powdered extracts are often produced by drying the extract onto an inert carrier, such as methyl cellulose, to facilitate processing into the final finished product.

#### 3.2.4.1 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 minimal thermal decomposition and chemical reactions (such as oxidation) to 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 applied technique for concentration, other approaches such as membrane technology and freeze concentration are available.

### 3.2.5 Fermentation
In some cases, herbal preparation is obtained after undergoing through a fermentation process of the plant powder 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 (e.g., *Lactobacillus* bacteria).

For natural fermentation, the dry plant powder, a decoction, or an extract of herbal material is often mixed with the juice of sugarcane, 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.

### 3.2.5.1 Fermentation procedures

- When fermentation is required to produce a herbal preparation, all utensils should be completely cleaned. A non-corrosive fermentor is required.
- The water to be used should comply with local requirement for potable water, not be alkaline and should be free of inorganic matters (deionized water).
- The temperature and length of fermentation should be optimized and controlled.
- When fermentation is complete, the solution is filtered and stored in suitable containers.

### 3.2.6 Powdering

*Content needs to be developed.*

We kindly request reviewers to provide us with suggested input, as well as, any relevant technical information for formulating description on this sub-section. Thank you very much.

#### 3.2.6.1 Powdering procedures

*Content needs to be developed.*

We kindly request reviewers to provide us with suggested input, as well as, any relevant technical information for formulating description on this sub-section. Thank you very much.

### 3.3 Documentation

The general principles for documentation are set out in the *GMP for pharmaceutical products: main principles* [WHO, 2007a – WHO, 2003b]; [WHO, 2014].

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 (scientific) name and the taxonomic authority (abbreviation if used should be according to internationally-accepted rules), the plant family name, any synonyms for the
4. GOOD HERBAL PROCESSING PRACTICES FOR THE PRODUCTION OF HERBAL DOSAGE FORMS

4.1 General information

In contrast to synthetic pharmaceutical drugs, many 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 Good Manufacturing Practices (WHO, 2007a). Starting materials for the preparation/production of various herbal dosage/final dosage forms should consist of good practice processed herbal materials or herbal preparations as described previously (Sections 2 and 3).

Examples of a number of herbal dosage forms are presented in the Japanese Pharmacopoeia (16th Edition) (see Annex 3).

The following describes some common dosage forms of herbal medicines.

4.2 Processing techniques and procedures
4.2.1 Liquid herbal dosage forms

Liquid herbal dosage forms as described herein pertains to oral preparations, including, but not limited to the following product types/categories:

4.2.1.1 Fluidextracts
For description, see section 3.2.3.

4.2.1.2 Infusions
For description, see section 3.2.3.

4.2.1.3 Decoctions
For description, see section 3.2.3.

4.2.1.4 Liquid (fluid) extracts
For description, see section 3.2.3

4.2.1.5 Tinctures
For description, see section 3.2.3

4.2.1.6 Syrups
Syrups are viscous liquid 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. When necessary, the mixture is boiled and filtered.

4.2.1.7 Oral emulsions
Oral emulsions are liquid oil-in-water preparations that are rendered homogeneous by the addition of emulsifying agent. For example, an oil obtained from herbs (e.g. castor oil) is dispersed in water and emulsified with an emulsifying agent such as gum acacia.

4.2.2 Solid herbal dosage forms

4.2.2.1 Herbal tea bags
Herbal tea bags are prepared by placing finely ground herbal materials (such as dried roots, leaves or flowers) into paper or cloth bags. When used, boiling water is poured into the vessel containing the bag to make an infusion.

4.2.2.2 Plant powders
Powders are prepared by grinding/pulverizing herbal materials to a suitable particle size.

4.2.2.3 Powdered extracts
Powdered extracts are 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.
4.2.2.4 Granules
Granules are dried liquid (fluid) extracts in the form of spherical particles. They are prepared by adding diluents, binders or other suitable excipients to extract powders, mixed to homogeneity and granulated by a suitable method. Typically, granules are dissolved in hot water to make a “herbal tea” for administration.

4.2.2.5 Pills
Pills are dried extracts or decoctions in the form of small, spherical solids, similar to granules. They may be prepared by adding suitable excipients to extract powders, mixed to homogenize and granulated by a suitable method. Typically, pills are swallowed with warm water.

4.2.2.6 Capsules
Capsules are prepared by enclosing herbal powder or dry/powder extract in capsule shells or in a suitable capsule base such as gelatine in a particular shape and size.

4.2.2.7 Tablets
Tablets are solid preparations having a defined shape and size. They are usually prepared by mixing the homogenous dry/powder extract with excipients such as diluents and binders, followed by compression into a defined shape and size.

4.2.2.8 Lozenges
Lozenges 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. In addition to herbal ingredient, lozenges often contain flavouring agents and sweetened bases.

4.2.3 Other herbal dosage forms

4.2.3.1 Ointments/creams
Ointments/creams are topical preparations for application to the skin. They are usually semi-solid emulsions dissolved or dispersed in a suitable base. Alongside with the herbal ingredients, they may contain emulsifiers or thickening agents.

4.2.3.2 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.

Dry powder inhalers are prepared by pulverizing dried extracts into fine particles. When necessary, lactose or other suitable excipients are added to make a homogenous mixture. Inhalation liquid preparations are usually prepared by mixing dried 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.

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

4.2.3.4 Aromatic waters
Aromatic waters are water preparations containing saturated essential oils or other volatile substances. Usually, an essential oil (1 part) is shaken in 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 have a characteristic odour of the essential oil or volatile substances used.

4.2.3.5 Gel capsules
Content needs to be developed.
We kindly request reviewers to provide us with suggested input, as well as, any relevant technical information for formulating description on this sub-section. Thank you very much.

5. TECHNICAL ISSUES SUPPORTING GOOD HERBAL PROCESSING PRACTICES

In the formulation of a good practice protocol for processing herbal materials, a number of supporting technical issues must be considered and adopted. Since the primary objective is to produce quality processed herbal materials and preparations, many of the same technical issues associated with the GACP, GMP and quality control (QC) methods are applicable to GHPP. Therefore, these guidelines have been consulted for applicable good practice items for adoption. Moreover, the same technical issues on 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 [WHO, 2003a]. Thus, the applicable good practice guidelines have been adopted in whole or modified as appropriate for the present guidelines.

5.1 Processing facilities
The ideal design and construction of a herbal material processing facility incorporating the most appropriate location, buildings, medicinal plant 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 [WHO, 2003a]. Therefore, they are adopted for the present guidelines and the descriptions are excerpted and presented in Annex 4 for easy reference.

5.2 Packaging and labelling
Processed herbal materials or herbal preparations should be packaged as quickly as possible to preserve their quality by preventing deterioration of the herbal medicines and to protect
against unnecessary exposure to pest infestations and other sources of contamination.

Continuous in-process quality control measures should be implemented to eliminate sub-standard materials, contaminants and foreign matter prior to and during the final stages of packaging. Processed medicinal plant materials should be packaged in clean, dry boxes, sacks, breathable bags or other containers in accordance with standard operating procedures and meeting national and/or regional regulations of the producer and the end-user countries. Materials used for packaging should be non-polluting, clean, dry and in undamaged condition and should conform to the quality requirements for the processed herbal materials or herbal preparations concerned. Fragile medicinal plant materials should be packaged in rigid containers. Wherever possible, the packaging used should be agreed upon between the supplier and buyer.

A label affixed to the packaging should clearly indicate the scientific name, usual common name, brand name, the processed plant part with date, the processing techniques used, the name and address of the processor, finished product manufacturer, importer or distributor, i.e. the entity who should be responsible for receiving consumer complaints and conducting a recall should the need arise, as well as information on the potency or strength of the medicinal ingredient if applicable (e.g., for an extract the drug extract ratio (DER) 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 number, and in the case of a prepared dosage form the quantity of each medicinal ingredient per dosage unit, list of excipients, recommended storage conditions, and expiry date. Retail labelling should also provide the recommended use or purpose, the recommended dose and frequency per day, recommended duration of use, and cautionary information (e.g., known side effects, warnings regarding interactions, contraindications). The label should also contain information indicating quality approval and compliance with other national and/or regional labelling requirements. The label should bear a number that clearly identifies the production batch.

Additional information about the production and quality parameters of the medicinal plant materials may be added in a separate certificate, which is clearly linked to the package carrying the same batch number.

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 materials or herbal preparations should be properly stored and preserved before use. They must be protected from microbial and insect contaminations, and rodents and other pests. Every effort should be tried to use the type of packaging that provides ample protection against physical damages to the materials and to keep away, as much as possible, from exposure to moisture, light, heat, and insect attack.

Substandard herbal medicines should be kept in a separate designated area, clearly labelled and with specified handling period. Toxic or specific herbal medicines 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 and herbal preparations with proper separation and segregation. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature and humidity limits, and controlled, monitored and recorded where appropriate to ensure good storage conditions.

Conveyances used for transporting processed herbal materials and herbal preparations from the place of processing to storage should be clean and, where appropriate, well ventilated to keep an appropriate level of air flow and to prevent condensation.

Fumigation against pest infestation in conveyances and in storage areas should be carried out only when necessary, and 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 materials should be checked after treatment.

**5.4 Equipment**

All equipment, including tools and utensils used in the processing of herbal materials and herbal preparations 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 hygienic 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 or recording devices.

**5.5 Quality assurance and quality control**

Quality assurance system is essential to ensure that herbal processing practice is consistently executed and controlled. Compliance with quality assurance measures should be verified through regular internal oversight personnel (QA manager) and external auditing visits to processing facilities by expert representatives of buyers and other stake holders and through
inspection by national and/or local regulatory authorities. No processed herbal material or processed herbal preparation shall be released until its quality complies or conforms with standard specifications.

5.6 Documentation

The SOP should be adopted and documented. All methods and procedures involved in the processing of herbal materials and herbal preparations 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 2.3.5 and 3.3 above. 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 according to their requirements.

5.7 Personnel

5.7.1 General

All personnel should receive proper post-harvest handling and herbal processing training. All personnel required to handle chemical solvents and adjuvants should receive adequate training and possess sufficient knowledge and appropriate techniques 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-processing and during processing handling of herbal materials should be trained and 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 toxic or potentially allergenic herbs by means of adequate protective clothing, including gloves and masks.

Health status

All personnel known, or suspected to be suffering from or to be a carrier of a disease or illness likely to be transmitted, should not 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 medicinal plant and processing/processed herbal materials and associated equipment including but not limited to: such as jaundice, diarrhoea, vomiting, fever, sore throat with fever, visibly infected lesions (boils, 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 who handle processing/processed herbal materials 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 medicinal plant materials or any contaminated material.

Smoking, drinking, and eating should not be permitted in medicinal plant 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 as traditional or historical methods is needed; Research to find alternate processing procedures to achieve the same therapeutic effect as traditional or historical methods is also needed. 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 also needed and encouraged.

Technical information resulting from processing method research 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 good herbal processing practices for individual medicinal plant part and document each in a monograph.

6.3 Adoption of good herbal processing practices

Member States or nations that have not adopted good herbal processing practices 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.

6.5 Threatened and endangered species

When obtaining medicinal plants 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 (CITES) have been complied with.

7. REFERENCES


Annex 1: Example of a model format of good herbal processing practices
monograph/SOP 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 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 ten *(WHO, 2011)*.

Quality testing of the raw material

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

The following requirements must be fulfilled:

- Morphology: Conform with the national pharmacopoeial standards
- Identification (including macroscopic, microscopic examination, 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**

 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 (HPLC) analysis**

Set up the 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 the plant material for processing

The source herbal materials are manually sorted by trained personnel according to the requirements specified in the SOP. Impurities (e.g. 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 guideline, 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 X 100%)

### 3.8 Cutting/sectioning/comminuting

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

The following requirements must be fulfilled.

- Non-conformed pieces: ≤ xxx %
- Powder fineness:
- Recovery: ≥ xxx %  (Recovery = Weight after cutting/Weight before cutting X 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 X 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 X 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.

#### 3.11.3 Storage

The packaged products must be stored in a clean, dry and well-ventilated area, at a constant 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.
Annex 2: Example of a model format of good herbal processing practices

monograph/SOP protocol to produce a herbal preparation

**TITLE of the monograph/protocol**

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

1. **Objective of the SOP 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 herb of 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. **Plant substance**
   
The identity of the raw plant material should be confirmed using morphological identification/validation by macroscopic and microscopic examinations and physicochemical tests by following the procedures set out in the pharmacopoeia or other authoritative documents.

   Specifications such as those below should be in place.

   - **Origins of the plant material (natural state/cultivation):** Describe appropriate origins of the plant material
   - **Plant part:** Describe the desired plant part/parts (i.e. flowers)
   - **Growing conditions:**
     - **Climatic conditions:** length of day, rainfall, field temperature (coldness/warmth)
     - **Soil conditions:** soil type, drainage/moisture retention, fertility
     - **Shade level**
     - **Fertilizers:** Specify allowable fertilizers in compliance with applicable regulations
     - **Pest controls:** Specify allowable pesticides and/or biological pest controls, in compliance with applicable regulations
   - **Fungicides:** Specify allowable fungicides (if any) in compliance with applicable regulations
   - **Fumigants:** Specify allowable fumigants (if any) in compliance with applicable regulations
   - **Harvest time:** Describe the appropriate months for harvest (i.e. during flowering (June-July))
   - **Harvesting:** Describe the process for harvesting (i.e. mechanical process)
   - **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 plant 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, harvesting site, net and gross weight and the name of the supplier.

5. **Processing**

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

<table>
<thead>
<tr>
<th>Raw Material/Function</th>
<th>Amount per 100 kg</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh X...y... herb</td>
<td>100.0 kg</td>
<td>Standard specification</td>
</tr>
<tr>
<td>Ethanol 95%</td>
<td>Xx litres</td>
<td>Pharmacopoeia .XYZ</td>
</tr>
<tr>
<td>Extraction water</td>
<td>quantum satis</td>
<td>Pharmacopoeia .XYZ</td>
</tr>
</tbody>
</table>

Raw materials accepted for processing must meet specifications for identity and quality. Specifications include appearance/description of the plant material(s), 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 the herb of X...y...

- **Step 1.** The fresh fragmented plant 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 plant material.

- **Step 2.** The stabilized plant 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 plant matter 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. **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. **Release specifications of final product**
Identify criteria that must be met for release of the final product. These criteria generally include appearance, relative density, and specified quantities for chemical constituent(s), as well as limits for heavy metals, microbial content 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.

8. **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.

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

10. **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.

11. **Storage conditions**
The packaged products must be stored in a clean, dry and well-ventilated area, at a constant 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.

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

13. **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.
Annex 3: Example of general rules for preparations/monographs of herbal preparations and herbal dosage forms


General Rules for Preparations/Monographs for Preparations Related to Crude Drugs

Monographs for Preparations Related to Crude Drugs

Preparations Related to Crude Drugs

(1) Preparations related to crude drugs are preparations mainly derived from crude drugs. Extracts, Pills, Spirits, Infusions and Decoctions, Teabags, Tinctures, Aromatic Waters, and Fluidextracts are included in this category.

Definitions, methods of preparations, test methods, containers and packaging, and storage of these preparations are described in this chapter.

(2) The descriptions of the test methods and the containers and packaging in this chapter are fundamental requirements, and the preparation methods represent commonly used methods.

1. Extracts

(1) Extracts are preparations, prepared by concentrating extractives of crude drugs. There are following two kinds of extracts.

   (i) Viscous extracts
   (ii) Dry extracts

(2) Unless otherwise specified, Extracts are usually prepared as follows.

   (i) Crude drugs, pulverized to suitable sizes, are extracted for a certain period of time with suitable solvents by means of cold extraction or warm extraction, or by percolation as directed in (ii) of (2) under 6. Tinctures. The extractive is filtered, and the filtrate is concentrated or dried by a suitable method to make a millet jelly-like consistency for the viscous extracts, or to make crushable solid masses, granules or powder for the dry extracts. Extracts, which are specified the content of active substance(s), are prepared by assaying active substance(s) in a portion of sample and adjusting, if necessary, to specified strength with suitable diluents.

   (ii) Weigh crude drugs, pulverized to suitable sizes, according to the prescription and heat for a certain period of time after adding 10 ÷ 20 times amount of water. After separating the solid and liquid by centrifugation, the extractive is concentrated or dried by a suitable method to make a millet jelly-like consistency for the viscous extracts, or to make crushable solid masses, granules or powder for the dry extracts.

(3) Extracts have odour and taste derived from the crude drugs used.

(4) Unless otherwise specified, Extracts meet the requirements of Heavy Metals Limit Test <1.07>$^1$

(for detail of test methods, procedure, and regents and solutions, see end note of this annex), when the test solution and the control solution are prepared as follows.

Test solution: Ignite 0.30 g of Extracts to ash, add 3mL of dilute hydrochloric acid, warm, and filter. Wash the residue with two 5-mL portions of water. Neutralize the combined filtrate and washings
(indicator: a drop of phenolphthalein TS) by adding ammonia TS until the color of the solution changes to pale red, filter where necessary, and add 2mL of dilute acetic acid and water to make 50mL.

Control solution: Proceed with 3mL of dilute hydrochloric acid in the same manner as directed in the preparation of the test solution, and add 3.0mL of Standard Lead Solution and water to make 50mL.

(5) Tight containers are used for these preparations.

2. **Pills**
   (1) Pills are spherical preparations, intended for oral administration.
   (2) Pills are usually prepared by mixing drug substance(s) uniformly with diluents, binders, disintegrators or other suitable excipient(s) and rolling into spherical form by a suitable method. They may be coated with a coating agent by a suitable method.
   (3) Unless otherwise specified, Pills comply with Disintegration Test.
   (4) Well-closed or tight containers are usually used for these preparations.

3. **Spirits**
   (1) Spirits are fluid preparations, usually prepared by dissolving volatile drug substance(s) in ethanol or in a mixture of ethanol and water.
   (2) Spirits should be stored remote from fire.
   (3) Tight containers are used for these preparations.

4. **Infusions and Decoctions**
   (1) Infusions and Decoctions are fluid preparations, usually obtained by macerating crude drugs in water.
   (2) Infusions and Decoctions are usually prepared by the following method.
     - Cut crude drugs into a size as directed below, and transfer suitable amounts to an infusion or decoction apparatus.
     - Leaves, flowers and whole plants: Coarse cutting
     - Woods, stems, barks, roots and rhizomes: Medium cutting
     - Seeds and fruits: Fine cutting
   (i) Infusions: Usually, damp 50 g of crude drugs with 50mL of water for about 15 minutes, pour 900 mL of hot water to them, and heat for 5 minutes with several stirrings. Filter through a cloth after cooling.
   (ii) Decoctions: Usually, heat one-day dose of crude drugs with 400 ñ 600mL of water until to lose about a half amount of added water spending more than 30 minutes, and filter through a cloth while warm. Prepare Infusions or Decoctions when used.
   (3) These preparations have odour and taste derived from the crude drugs used.
   (4) Tight containers are usually used for these preparations.

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5. Tea bags
(1) Tea bags are preparations, usually packed one day dose or one dose of crude drugs cut into a size between coarse powder and coarse cutting in paper or cloth bags.

(2) Teabags are usually used according to the preparation method as directed under 4. Infusions and Decoctions.

(3) Well-closed or tight containers are usually used for these preparations.

6. Tinctures
(1) Tinctures are liquid preparations, usually prepared by extracting crude drugs with ethanol or with a mixture of ethanol and purified water.

(2) Unless otherwise specified, Tinctures are usually prepared from coarse powder or fine cuttings of crude drugs by means of either maceration or percolation as described below.

   (i) Maceration: Place crude drugs in a suitable container, and add an amount of a solvent, equivalent to the same volume or about three-fourths of the volume of the crude drugs. Stopper container, and allow the container to stand for about 5 days or until the soluble constituents have satisfactorily dissolved at room temperature with occasional stirring. Separate the solid and liquid by centrifugation or other suitable methods. In the case where about three-fourths volume of the solvent is added, wash the residue with a suitable amount of the solvent, and squeeze the residue, if necessary. Combine the extract and washings, and add sufficient solvent to make up the volume. In the case where the total volume of the solvent is added, sufficient amounts of the solvent maybe added to make up for reduced amount, if necessary. Allow the mixture to stand for about 2 days, and obtain a clear liquid by decantation or filtration.

   (ii) Percolation: Pour solvent in small portions to crude drugs placed in a container, and mix well to moisten the crude drugs. Stopper container, and allow it to stand for about 2 hours at room temperature. Pack the contents as tightly as possible in an appropriate percolator, open the lower opening, and slowly pour sufficient solvent to cover the crude drugs. When the percolate begins to drip, close the opening, and allow the mixture to stand for 2 to 3 days at room temperature. Then, open the opening, and allow the percolate to drip at a rate of 1 to 3mL per minute. Add an appropriate quantity of the solvent to the percolator, and continue to percolate until the desired volume has passed. Mix thoroughly, allow standing for 2 days, and obtain a clear liquid by decantation or filtration. The time of standing and the flow rate may be varied depending on the kind and amount of crude drugs to be percolated.

Tinctures, prepared by either of the above methods and specified the content of marker constituent or ethanol, are prepared by assaying the content using a portion of the sample and adjusting the content with a sufficient amount of the percolate or solvent as required on the basis of the result of the assay.

(3) Tinctures should be stored remote from fire.

(4) Tight containers are used for these preparations.

7. Aromatic Waters
(1) Aromatic Waters are clear liquid preparations, saturated essential oils or other volatile substances in water.

(2) Unless otherwise specified, Aromatic Waters are usually prepared by the following process. Shake
thoroughly for 15 minutes 2 mL of an essential oil or 2 g of a volatile substance with 1000 mL of lukewarm purified water, set the mixture aside for 12 hours or longer, filter through moistened filter paper, and add purified water to make 1000 mL. Alternatively, incorporate thoroughly 2 mL of an essential oil or 2 g of a volatile substance with sufficient talc, refined siliceous earth or pulped filter paper, add 1000 mL of purified water, agitate thoroughly for 10 minutes, and then filter the mixture. To obtain a clear filtrate repeat the filtration if necessary, and add sufficient purified water passed through the filter paper to make 1000 mL.

(3) Aromatic Waters have odour and taste derived from the essential oils or volatile substances used.

(4) Tight containers are used for these preparations.

8. Fluidextracts

(1) Fluidextracts are liquid percolates of crude drugs, usually prepared so that each mL contains soluble constituents from 1 g of the crude drugs. Where the content is specified, it takes precedence.

(2) Unless otherwise specified, Fluidextracts are usually prepared from coarse powder or fine cutting of crude drugs by either of following maceration or percolation.

(i) Maceration: Place a certain amounts of crude drugs in a suitable vessel, add a solvent to cover the crude drugs, close the vessel, and allow the vessel to stand at room temperature with occasional stirring for about 5 days or until the soluble constituents have satisfactorily dissolved. Separate the solid and liquid by centrifugation or other suitable method. Usually, reserve a volume of the liquid equivalent to about three-fourths of the total volume, and use it as the first liquid. Wash the residue with appropriate amount of the solvent, combine the washings and the remaining of the first liquid, concentrate if necessary, mix with the first liquid, and use it as solution (A). To the solution (A) add the solvent, if necessary, to make equal amount of the mass of the crude drugs. Allow the mixture to stand for about 2 days, and collect a clear liquid by decantation or filtration.

(ii) Percolation: Mix well 1000 g of the crude drugs with the first solvent to moisten them, close the container, and allow it to stand for about 2 hours at room temperature. Transfer the content to a suitable percolator, stuff it as tightly as possible, open the lower opening of the percolator, and slowly pour the second solvent to cover the crude drugs. Close the lower opening when the solvent begins to drop, and allow the mixture to stand for 2 to 3 days at room temperature. Open the lower opening, and allow the percolate to run out at the rate of 0.5 to 1.0 mL per minute. Set aside the first 850 mL of the percolate as the first percolate. Add the second solvent to the percolator, then drip the percolate, and use it as the second percolate.

The period of standing and the flow rate during percolation may be varied depending on the kind and the amount of crude drugs used. The flow rate is usually regulated as follows, depending on the using amount of crude drugs.

<table>
<thead>
<tr>
<th>Mass of crude drug</th>
<th>Volume of solution running per minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not more than 1000 g</td>
<td>0.5 - 1.0 mL</td>
</tr>
<tr>
<td>Not more than 3000 g</td>
<td>1.0 - 2.0 mL</td>
</tr>
<tr>
<td>Not more than 10000 g</td>
<td>2.0 - 4.0 mL</td>
</tr>
</tbody>
</table>

Concentrate the second percolate, taking care not to lose the volatile substances of the crude drug, mix with the first percolate, and use it as solution (A). To the solution (A) add the second solvent to make...
1000 mL, and allow the mixture to stand for about 2 days. Decant the supernatant liquid or filter the liquid to obtain a clear solution.

Fluidextracts for which the content of marker constituent or ethanol is specified are obtained by adjusting the content with a sufficient amount of the second solvent as required on the basis of the result of the assay made with a portion of the solution (A).

(3) Fluidextracts have odour and taste derived from the crude drugs used.

(4) Unless otherwise specified, Fluidextracts meet the requirements of Heavy Metals Limit Test <1.07> when the test solution and the control solution are prepared as follows.

Test solution: Ignite 1.0 g of Fluidextracts to ash, add 3 mL of dilute hydrochloric acid, warm, and filter. Wash the residue with two 5-mL portions of water. Neutralize the combined filtrate and washings (indicator: a drop of phenolphthalein TS) by adding ammonia TS until the colour of the solution changes to pale red, filter if necessary, and add 2 mL of the dilute acetic acid and water to make 50 mL.

Control solution: Proceed with 3 mL of dilute hydrochloric acid in the same manner as directed in the preparation of the test solution, and add 3.0 mL of Standard Lead Solution and water to make 50 mL.

(5) Tight containers are used for these preparations.

*Test <1.07> 1.07 Heavy Metal Limit test (JP 16, pp21-23)*

Heavy Metals Limit Test is a limit test of the quantity of heavy metals contained as impurities in drugs. The heavy metals are the metallic inclusions that are darkened with sodium sulfide TS in acidic media, as their quantity is expressed in terms of the quantity of lead (Pb). In each monograph, the permissible limit for heavy metals (as Pb) is described in terms of ppm in parentheses.

Procedure:

Add 1 drop of sodium sulfide TS to each of the test solution and the control solution, mix thoroughly, and allow to stand for 5 minutes. Then compare the colors of both solutions by viewing the tubes downward or transversely against a white background. The test solution has no more color than the control solution.

Solutions and Reagents:

**Standard Lead Solution**

Measure exactly 10 mL of Standard Lead Stock Solution, and add water to make exactly 100 mL. Each mL of this solution contains 0.01 mg of lead (Pb). Prepare before use.

**Standard Lead Stock Solution**

Weigh exactly 159.8 mg of lead (II) nitrate, dissolve in 10 mL of dilute nitric acid, and add water to make exactly 1000 mL. Prepare and store this solution using glass containers, free from soluble lead salts.

**Ammonia solution (28)**

NH₄OH [K 8085, Ammonia Water, Special class, Density: 0.90 g/mL, Content: 28-30%]

**Ammonia TS**

To 400 mL of ammonia solution (28) add water to make 1000 mL (10%).

**Acetic acid, dilute**

Dilute 6 g of acetic acid (100) with water to make 100 mL (1 mol/L).

**Acetic acid (100)**

CH₃COOH [K 8355, Acetic Acid, Special class]

Dilute acetic acid

See acetic acid, dilute.
Dilute hydrochloric acid
See hydrochloric acid, dilute.

Hydrochloric acid, dilute
Dilute 23.6 mL of hydrochloric acid with water to make 100mL (10%).

Hydrochloric acid
HCl [K 8180, Special class]

Phenolphthalein TS
Dissolve 1 g of phenolphthalein in 100 mL of ethanol (95).

Phenolphthalein
C20H14O4 [K 8799, Special class]

Ethanol (95)
C2H5OH [K 8102, Special class]

Sodium sulfide enneahydrate
Dissolve 5 g of sodium sulfide enneahydrate in a mixture of 10 mL of water and 30 mL of glycerin. Or dissolve 5 g of sodium hydroxide in a mixture of 30 mL of water and 90 mL of glycerin, saturate a half volume of this solution with hydrogen sulfide, while cooling, and mix with the remaining half. Preserve in well-filled, light-resistant bottles. Use within 3 months.

Sodium hydroxide
NaOH [K 8576, Special class]

Glycerin
C3H8O3 [K 8295, Glycerol, Special class. Same as the monograph Concentrated Glycerin]

Hydrogen sulfide
H2S Colorless, poisonous gas, heavier than air. It dissolves in water. Prepare by treating iron (II) sulfide heptahydrate with dilute sulfuric acid or dilute hydrochloric acid. Other sulfides yielding hydrogen sulfide with dilute acids may be used.

Sulfuric acid
H2SO4 [K 8951, Special class]

Sulfuric acid, dilute
Cautiously add 5.7 mL of sulphuric acid to 10 mL of water, cool, and dilute with water to make 100 mL (10%).

Iron (II) sulfate heptahydrate
FeSO4.7H2O [K 8978, Special class]
Annex 4: Processing facilities

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).

4.1 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;
- to ensure the logical flow of materials and personnel;
- 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.

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, and 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.