Annex 7

Good pharmacopoeial practices: Chapter on monographs on herbal medicines

Background

Following the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidance on good pharmacopoeial practices (GPhP) was published as Annex 1 to the report.[1] The primary objective of the GPhP is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization. In line with this objective, this guidance for monographs on herbal medicines has been developed outlining the structure and contents of a herbal medicine monograph.

1. Introduction

Pharmacopoeial monographs for herbal medicines should contain information in the definition that is consistent with the monograph title, followed by specifications for quality including identity, purity and content. Individual monographs describe test procedures, together with the corresponding specifications. The monograph may include:

- an official title;
- a definition;
- a production section;
- an identification section;
- a test section covering, for example, physicochemical tests and, where appropriate, tests on contaminants;
- an assay section on determining constituents with known therapeutic activity, active or analytical markers.

Further sections providing information on labelling and storage may also be provided.

[1] Good pharmacopoeial practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

2. General chapter

The general testing methods and other specifications that are common for herbal medicines may be described in a General chapter.

3. Individual monographs on herbal medicines

3.1 Monograph title

The title of the monograph may include the Latin name, or the well-established common local name and English common name. This may be followed by the name of relevant plant part(s) or plant material (e.g. resin, gum-resin) and, where applicable, its state and the type of herbal preparation (e.g. liquid extract, dry extract) and its dosage form (e.g. tablet, capsule or other form). Individual pharmacopoeias may apply their own nomenclature policies that meet regulatory needs and reflect the common names in commerce, as appropriate.

3.2 Definition

The definition provides details about the subject of the monograph and includes: the Latin binomial name and the taxonomic authority (abbreviations, if used, should be according to internationally accepted rules); the plant family name, if required by national legislation; the well-established common local name and English common name may be provided in addition to the scientific name, together with well-recognized synonyms. This section also provides details about the plant part(s) (i.e. aerial parts, root, leaves, flowers, rhizome, etc.), plant material (e.g. resin, gum-resin) and, where applicable, its state and the type of herbal preparation (e.g. liquid extract, dry extract) and its dosage form (tablet, capsule, etc.). When necessary, as dictated and supported by data, the definition also states the season or period in which plant material should be harvested according to *Good agricultural and collection practices (GACP) for medicinal plants*.[2] If more than one species is covered by the monograph, the definition should include, for each of the species, the requirements listed above. The definition should include the names and molecular formulae of relevant known constituents for which there is a specified range or minimum content, in percentages, usually calculated on the basis of the dry weight of the herbal medicine. Where a monograph applies to the herbal medicine in different states or stages of processing, this is stated in the definition.

[2] WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva: World Health Organization; 2003.

3.3 Identification

The purpose of the Identification section is to ensure that the herbal medicine under examination is the one stated on the label. It is only necessary to include those techniques that are applicable for the identification of specific herbal medicines. Macroscopic and microscopic descriptions may be supported by illustrations. Identification tests should be specific for the herbal medicine under examination. Typically, several identification tests, using independent approaches, are required in order to confirm the identity. The tests given in the Identification section are not designed to give a full confirmation of the chemical structure or composition of the herbal medicine. They are intended to give confirmation, with an acceptable degree of assurance, that it is the one stated on the label.

Test methods should be able to detect substitutes or adulterants that are likely to be found.

3.3.1 Macroscopic characteristics

The important macroscopic botanical characteristics of the herbal materials are specified to enable a clear identification. Where two or more species of a genus or subspecies are included in the definition, the differences, if any, between them should be indicated.

3.3.2 Microscopic characteristics

The microscopic examination of herbal materials is useful in determining their identity. Histological characteristics, such as microscopic characteristics of a transverse or longitudinal section may support the identification. For herbal materials for which macroscopic identification cannot be performed (for example, powdered herbal materials), the microscopic characteristics are important to determine their identity.

3.3.3 Chemical tests

Chemical tests can also be useful in determining the presence of substitution, adulteration or other foreign matter. Nonspecific chemical tests should be avoided. Phytochemical screening tests that recognize general classes of compounds such as alkaloids, flavonoids, terpenes, steroids, saponins and tannins, among others, should be avoided unless they provide a means of identifying potential adulteration due to species substitution or adulteration.

3.3.4 Fingerprinting

Chromatographic or spectroscopic patterns, often referred to as "fingerprints", may be used for identification. The fingerprints should ideally be able to

distinguish the herbal material under examination from other species that constitute both intentional and unintentional adulterants.

Fingerprints may be obtained, for example, by thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), high-performance liquid chromatography, ultra-high-performance liquid chromatography, capillary electrophoresis or gas chromatography methods. The methods should include all of the information required to perform the test, for example, preparation of sample and reference solutions, nature of plates or columns, testing conditions, mobile phase preparation, flow rate, and method of detection/detectors.

The results of such testing should contain a description of the critical features of the fingerprint chromatograms, such as the presence of specific peaks, bands or spots, retention time or relative retention values, retardation or retention factor (RF or Rf), their order of elution and, where applicable, their relative abundance. A colour image of a typical reproducible TLC fingerprint and/or table presentation may be provided as a guide for users. Pharmacopoeias may consider providing reference standards (RS) to be used for fingerprint testing.

3.3.5 DNA-based tests

DNA-based tests, such as polymerase chain reaction and DNA sequencing, can be useful in identifying specific herbal materials or detecting adulteration with either related or unrelated species that are difficult to detect using other methods.

3.4 Tests for contaminants/impurities

3.4.1 General

Tests for the following may be included and limits specified, as appropriate:

- foreign matter;
- elemental contaminants or impurities (for example, toxic metals such as lead, cadmium, mercury and arsenic);
- microbiological quality: individual pharmacopoeias may consider specifying requirements for total aerobic microbial count and total combined yeast/moulds count as well as for specified microorganisms, for example, bile-tolerant Gram-negative bacteria, *Escherichia coli* and *Salmonella*;
- mycotoxins;
- toxic and harmful substances (such as pesticide residues, radioactive contaminants and natural toxins);
- residual solvents.

3.4.2 Specific

An individual herbal medicine may require specifications that are peculiar to that item, especially when patient safety is an issue. Limits should be set for certain constituents of the herbal medicines that may be considered undesirable "negative markers", negative botanical characteristics or histological parameters.

For some individual herbal medicines, there could be a risk of adulteration by herbal medicines that have a related morphological appearance or are marketed under similar common names. In such cases, additional tests may be specified, as appropriate, to detect and determine such adulterants. Where appropriate, tests for compounds that may affect the safety of the herbal medicines (such as alkaloids or cardiotonic steroids, among others) may be included in the monograph.

3.5 Assay

Where the constituent(s) responsible for the therapeutic activity of the herbal medicine is/are known, its/their quantitative determination should be included. Where the chemical constituent(s) responsible for the known therapeutic activity is/are not known, the pharmacopoeia may include testing for determination of the chemical constituent(s) that act as analytical or active marker(s).

Where an assay of one or more chemical constituents is carried out, assay limits are specified for each constituent either as a minimum content or as a percentage content range. Where the herbal medicine contains constituents that are known to degrade (e.g. due to improper drying, storage under high temperatures or extended storage), those constituents may be used as analytical markers to control the quality of the herbal medicine.

Stability-indicating chromatographic procedures that are validated for routine quality control work should be used, where possible. Pharmacopoeial procedures should be validated in accordance with accepted scientific practice and current recommendations on analytical validation. Assay methods developed through a collaborative process involving several laboratories, or using other suitable approaches, may be adopted.

3.6 Physicochemical tests

Physicochemical tests can serve as a valuable source of information and provide appropriate characterization standards to establish the quality of herbal medicines. Such evaluations may include:

- water and/or alcohol extractable matter;
- total ash content;
- water-soluble ash;

- alcohol-soluble ash;
- acid-insoluble ash;
- loss on drying;
- water content;
- volatile oils, etc.

3.7 Other tests

The following tests may be included, as appropriate:

- swelling index;
- bitterness values;
- particle size;
- any other test(s) specific to the particular herbal medicine.

Reference to taste and/or odour in the definition or the test procedures may be inappropriate due to safety reasons and should be avoided.

3.8 Additional information

3.8.1 Packaging, labelling and storage

Labelling requirements consistent with applicable national or regional legislation may be provided. Storage conditions may be provided when considered necessary to prevent contamination and/or to minimize possible deterioration. Guidance statements specifying the packaging may be included, where applicable, for example, in monographs for oils or oleoresins or distilled oils.

3.8.2 Reference standards

Pharmacopoeias may describe the use of RS in the analysis of individual herbal medicines. RS may be pure substances or extracts of herbal materials or powdered herbal materials used for comparison. The RS established by individual pharmacopoeias are suitable for their intended purpose.

Glossary

To comply with national and regional legislation, the definitions given in the individual pharmacopoeias may deviate from those provided below.

Adulterant is herbal material, a herbal constituent or other substance that is either deliberately or non-intentionally (through cross-contamination or contamination) added to a herbal material, herbal preparation or finished herbal product.

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

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

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, fungi, algae or lichens).

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

Herbal materials[3] include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other plant materials.

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

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made from 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

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

substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be "herbal".

Medicinal plant materials: see Herbal materials

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

State of the herbal material means whole, fragmented, peeled, cut, fresh or dried.