

**Monographs in the *Herbal Medicines Compendium*
Guidelines Document
Version 1.1: Feb 03, 2015**

This document provides guidance to sponsors of herbal articles for inclusion in the *Herbal Medicines Compendium (HMC)*. See General notices for articles deemed appropriate for inclusion in *HMC*.

Sections & subsections of a Monograph

Monograph sections of *HMC* address specifications with respect to identity, purity, quality, and strength for the article. The following information under each section of the monograph for *HMC* shall be provided for each herbal article. The monograph sections are Authorized Title, Definition, Identification, Composition, Contaminants, Specific Tests, and Additional Requirements.

Authorized Title

For monographs intended for inclusion in *HMC*, the title of the monograph includes the Latin binomial without the authority followed by the name of the plant part(s) or plant product (e.g., latex, exudates, resin, gum-resin, oleo gum resin), and wherever applicable the processed form. The plant part, plant product, and processed form names are written in English. In cases where more than one but not all species are represented in the monograph, the genus name will be used followed by the word “species.” Additional information such as the specific species and the complete Latin binomial including the authority of the will be included under the definition. See Guideline for Assigning Titles to USP *Herbal Medicines Compendium* Monographs.

Definition

The following information shall be provided for the herbal article: the Latin binomial, the taxonomic authority abbreviation, the plant family name, the plant part(s) (i.e., aerial parts, root, stem bark, root bark, leaf, flower, rhizome, etc.), plant product (e.g., latex, resin, oleo-gum resin, gum resin, exudate etc.), and where applicable the processed form. When necessary as dictated and supported by data, the Definition must state the season or period of harvest/collection of the plant material. In case a submission includes more than one species, the Definition must include, for each of the species, the requirements listed above. In addition, the Definition must include the chemical names, and/or molecular formulas of relevant known constituents, for which there is a specified minimum content, in percentage, usually calculated on the basis of the dry weight of the herbal article.

Identification

The purpose of the Identification section of a monograph is to ensure that the article under examination is in agreement with what is stated in the Definition of the article. The information under the categories of Authorized Title, Definition, and Additional Requirements-Labeling must be in agreement with the tests included in the Identification Category. This section usually includes several tests that complement each other. Together, these tests not only serve to ensure the accurate identification of the article, but also are able to distinguish the plant material from related species that may pose potential problem for species substitution or adulteration. Substitutions may arise from similar common names including those in the language spoken in the region of origin, plants that share similar botanical descriptions, taxonomic ambiguities, or confusion with other species from the same genus. Tests most commonly included in this section are described below.

Macroscopic and Microscopic Requirements

Focus must be on those characteristics that are unique to the species subject of the monograph, or are helpful to differentiate the article from related species, here termed “diagnostic macro/microscopic features” cited as requirements for the identification. Macroscopic and microscopic requirements of an herbal article must be provided in detail with color photographs. Typical structures to be described and their usual characteristics are listed in the General Chapter <563> *Identification of Articles of Botanical Origin*. This chapter provides information on the common techniques for mounting and staining herbal tissues or powdered material for microscopic examination. Organoleptic characteristics are not part of the identification tests. They may be useful and descriptive properties of an herbal article. However, organoleptic characteristics are not meant to be applied as tests for identifying materials. *HMC* monographs do not specify taste. *HMC* monographs may provide information about odor but no particular reference to odor will be made for materials known to pose a safety concern if inhaled. The words “characteristic odor” may be used to describe the odor characteristic of an herbal article that is considered innocuous. Differentiating pharmacognostic features of the genuine article along with diagnostic features of the adulterants/substituents wherever reported should be given to understand how it can be distinguished from the authentic sample.

Some detailed microscopic requirements are as follows:

- Roots and rhizomes (transverse sections)
Diagnostic features should be given in a systematic order starting from the periphery to the center. Details to be mentioned may be the following: arrangement of the vascular bundles and the type of vascular bundles; type and thickenings of vessels and fibers; width and nature of medullary rays; presence or absence of stone cells, and when present, shape and size of the same; type of cork cells; endodermal layer and nature of its cells and cell walls; type, shape and size of starch grains, hilum positions, striations; type and form of calcium-oxalate crystals.
- Barks (transverse section)
Details of periderm, which includes phellem, phellogen and phelloderm; cortex and its cellular content; phloem fibers, if any; stone cells (sclereids) when present; type of calcium-oxalate crystals when present; width of medullary rays, such as biseriate, multiseriate.
- Woods (Transverse section)

- Type of vessels/vessel elements and thickening; width of medullary rays, such as biseriate, multiseriate; type of fibers; type of crystals.
- Leaves (transverse section)
 - Whether a leaf is dorsiventral or isobilateral; if trichomes present, then their type and form; type of stomata; epidermal layer with its cells; arrangement of palisade and spongy parenchyma; details of midrib; excretory or secretory cells, if present.
- Leaves (surface view)
 - Trichomes, stomata, cuticle, epidermal cells shape, epidermal cells walls.
- Flowers
 - Normally no transverse sections are required for flowers. Vertical sections may be necessary to describe the requirements for flowers. Transverse sections of anthers and/or ovaries may be required if necessary.
- Fruits and seeds
 - The outer covering of the fruit i.e. pericarp is distinguished into outer epicarp, middle mesocarp, and inner endocarp. The outermost layer of seed is the testa, which encloses the endosperm. Shape and cellular content of endosperm and type of endosperm and embryo are of importance, besides the epidermal layer of the testa and other neighboring layers.

Chemical Tests

Chemical methods involving chemical reactions contribute to the identification of herbal article. Chemical tests such as color tests that are useful to differentiate the subject species from articles having potential for substitution/adulteration may be considered. Nonspecific chemical tests must be avoided. Phytochemical screening type tests that recognize general classes of compounds such as alkaloids, flavonoids, terpenes, steroids, saponins, tannins, and so on, must be avoided, unless they provide a mean to differentiate potential adulteration due to species substitution/adulteration.

Chromatographic and Other Separation Tests

Chromatographic fingerprint methods, such as thin-layer, liquid, or gas chromatography, are required to be accompanied by chromatograms/figures showing separation of the components of interest.

Chromatographic tests require the presence of characteristic constituents useful for identification of a plant material, either as marker compounds or as active principles as described in the General Chapter <563> *Identification of Articles of Botanical Origin*. After examination of a sufficient number of batches of authentic herbal material by chromatographic techniques from more than one source, at least one of these sources should be representative of material harvested from the plant's native origin and determined to be of the quality traditionally used in that region, it should be possible to choose those characteristic markers for identification.

Negative markers that are indicators of species substitution or contamination may also be specified. In addition to the identification using specified markers, chromatographic identification may be achieved by describing chromatographic fingerprints without specific mention of markers. However, these fingerprints should employ measures for referencing of the chromatographic peaks or bands to known compounds.

Chromatographic or spectroscopic patterns, sometimes referred to as "fingerprints", may be used as standards for identification, provided the acceptance ranges for specified

characteristics of these patterns are included in this section. These fingerprints can be obtained by HPLC, UHPLC, capillary electrophoresis, GC, TLC/HPTLC, NIR, IR, Raman, NMR, and/or MS. The acceptance ranges for fingerprinting tests must be set so they include allowed variability between different suppliers and different samples of the authentic article acquired under various conditions. The fingerprints must be able to distinguish these materials from other materials having potential for species substitution and those having a proven record of toxic effects or other safety and efficacy issues.

The acceptance criteria for identification tests using chromatographic methods such as HPLC, UHPLC, capillary electrophoresis or GC methodology must contain a description of the critical features of the fingerprint chromatograms such as the presence of specified peaks, their order of elution, and where possible, their relative abundance. To the extent possible, efforts to assign these peaks to known constituents must be performed. Acceptance criteria for peak ratios and elution order should be determined taking into account the variability associated with the standardized compendial article. Under the methods of TLC/HPTLC, description must include color and position of the characteristic bands. A color image of a typical HPTLC chromatogram is provided.

A critical aspect of the identification of herbal material by separation techniques is the use of reference standards because they provide assignment at the time of use. In addition to the *Sample solution*, a *Standard solution* containing the reference standard is chromatographed concomitantly. The reference material used in the *Standard solution* may be an Authenticated Botanical Reference Standard (BRS), an Extract Reference Standard (ERS). Highly purified single Phytochemical Reference Standard (PRS) entities are the best reference standards to provide more defined assignment of loci in complex chromatograms, and this approach will be preferred, if those substances are available and affordable. However, reference standards for single chemical entities of products of secondary metabolism of plants are often difficult to develop or prohibitively expensive, or both. In those cases, the USP approach to loci identification in complex chromatograms includes the use of a USP complex standard such as USP Reference Standard Extract, USP standardized mixture of substances or USP Authenticated Botanical Reference Standard. These USP complex standards are fully analyzed in collaborative studies under the chromatographic conditions described in the monograph, and being associated to a “USP Reference Chromatogram” with peaks of interest labeled. Each lot of these USP complex standards is supplied with its own USP Reference Chromatogram to overcome the batch-to-batch variability that may arise. Typically, as a System Suitability Test (See General Chapter <621> *Chromatography*), analysts are required to inject or apply a *Standard solution* containing the appropriate USP complex standard and reproduce the accompanying USP Reference Chromatogram under the actual analytical conditions of use, utilizing their own chromatographic systems. Adjustments to the chromatographic conditions may be needed in order to obtain a chromatogram similar to the “USP Reference Chromatogram,” thus achieving the suitability of the system for the chromatographic conditions described in the monograph. Once the system suitability has been established, the analysts would be able to assign the actual loci of the relevant markers or active principles in their own analytical systems by comparison with the USP Reference Chromatogram of the corresponding lot of USP complex standard. *Sample solutions* containing the samples being analyzed are then chromatographed for identification purposes. In HPTLC, the color and position of bands obtained with USP reference standards are used to define system suitability tests to be met on each plate.

Identification of herbal articles using spectroscopic methods must involve the collection of spectra of the samples appropriately prepared for the method in use. Acceptance criteria may be defined in terms of a set of authentic reference materials encompassing the accepted variability for the material to define the acceptance range.

Composition

Where the chemical constituents responsible for a known pharmacological/therapeutic activity for the herbal article are known, *HMC* monograph always includes a quantitative determination for these active principles under the section “Assay.” In the absence of definitive information on the active principle(s) present in the herbal material, sufficient information must be provided to USP regarding marker substance(s) chosen to monitor the quality of the herbal article. The preference is to use pharmacologically/therapeutically active markers over analytical markers as defined in the General Chapter <563> *Identification of Articles of Botanical Origin*. USP prefers to use stability-indicating chromatographic procedures that are validated for routine quality control work.

HMC monographs in most cases include analytical procedures for more than one phytochemical marker or group of phytochemical markers. Selection of markers for quantitative purposes must be made taking in consideration the potential adulteration by the addition of such markers from external sources. Analytical markers used for this purpose should not be ubiquitous in plants except in cases where the content of such markers are distinctively higher than their occurrence in other plants. Any phytoconstituent having reported toxicity must be used as a negative marker reporting its absence or not more than limits of safety. For these reasons, determination of multiple markers, giving typical profiles, and if possible from different phytochemical classes, (e.g., flavonoids, iridoids, terpenes, phenylpropanoids, alkaloids, etc.) is preferred over the determination of a single component.

The submission for *HMC* monographs must contain the following information, including all literature references where possible:

- Chemical names, structures, and molecular formulas of all known constituents.
- Validated analytical procedures for all the phytochemical reference marker(s) with supportive chromatograms and validation data following the General Chapter <1225> *Validation of Compendial Methods*. The analytical method must be capable of detecting degradants wherever required.

Contaminants—General

Microbial Limits

It is well known that herbal articles generally are contaminated with a great number of bacteria and molds arising from the soil and surrounding environment. In addition, further contamination results from harvesting/postharvest practices. A good indicator of

compliance with Good Agricultural and Collection Practices comes from a determination of absence of *E. coli* and yeasts and molds counts.

It is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present including microbial contamination. Thus, *HMC* monographs should not be expected to specify tests for every known microorganism. However, *HMC* monographs should specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific pathogenic bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella* species). These must be suitably determined using compendial procedures specified in the General Chapter <61>*Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and General Chapter <62>*Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*. Specifications for other microorganisms such as aflatoxins, where identified, must be provided with validation data for the analytical procedures used.

Aflatoxins

Aflatoxins are one of the most toxic classes of mycotoxins that arise from the growth of many species of *Aspergillus*. Wherever fungal contamination of the herbal article is likely, it is advisable to include a test for aflatoxins as described in the General Chapter <561>*Articles of Botanical Origin* to ensure that the tolerable limit has not been exceeded.

Heavy Metals

Heavy metals may be present in herbal articles as a consequence of natural occurrence or from human activities such as industrial waste in the soil, irrigation with contaminated water or airborne pollution. In addition, post-harvesting practices such as drying and milling operations could account for contamination of herbal materials with heavy metals. Compendial tests are provided to demonstrate that the content of metallic impurities does not exceed the heavy metals limits specified in the individual monograph. It is important to achieve selectivity towards only toxic metals distinguishing from those that are naturally occurring and have no relevant toxicity at the concentrations typically found in herbal article (e.g. inorganic versus organic arsenic). General procedures for the determination of specific metals are described in the General Chapter <233>*Elemental Impurities- Procedures*.

Pesticides

Herbal articles may become exposed to pesticides during cultivation or from the surrounding environment. An enormous variety of pesticides is used in different regions and nations all over the world. General expectations now in worldwide commerce, as reflected in the World Health Organization (WHO) guidelines, are that when such items are imported, the country of origin must be specified in order to understand the type of pesticides normally used in the country of origin.

The designation *pesticide* applies to any substance or mixture of substances intended to prevent, destroy, or control any pest, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport, or marketing of pure articles. The designation includes substances intended for use as growth regulators, defoliants, desiccants, and any substance applied to crops before or after harvest to protect the product from deterioration during storage and transport.

If no limits for pesticides exist, the limits must be below the detection limit of the specified method. The limits contained in the General Chapter <561>*Articles of Botanical Origin*, are not applicable in the United States when articles of herbal origin are labeled for food purposes. The limits, however, may be applicable in other countries where the presence of pesticide residues is permitted.

Contaminants—Special

An individual herbal article may require specifications that are peculiar to that item, especially when safety is an issue. One may set limits on certain constituents of the article that may be considered undesirable “negative markers” negative botanic characteristics or histological parameters. An example of this is a limit for ginkgolic acids in ginkgo extract. When one desires a limit for harmful substances that are present either naturally in the article or formed as a result of post-harvest processing practices, such submissions must be accompanied by toxicity data.

Specific Tests

Regarding foreign organic matter, *HMC* monographs are specific in defining the article by stating the plant part(s) (e.g., leaves, flowers, etc.) or plant product(s) (e.g., resins, gums, etc.) used. This, therefore, necessitates specifying a visual test and limits for excluding with plant parts other than the plant part described in the definition of the article such as twigs and stems are considered as foreign matter if the drug is defined as leaf. Furthermore, the common adulterants are other related species belonging to the same genus and family or other unrelated species or weeds. *HMC* monographs generally follow the procedure outlined in General Chapter <561>*Articles of Botanical Origin*.

There is general agreement among various pharmacopeias and the WHO that certain general quality parameters must apply to most, if not all, herbals. These are reflected in the tests for *Total ash*, *Residue on ignition*, and *Acid-insoluble* or *Water-soluble ash*, or both. Submissions must be based on requirements provided in the General Chapter <281>*Residue on Ignition* and General Chapter <561>*Articles of Botanical Origin*.

Limits on moisture and volatiles are obvious monograph requirements, and the general tests requirements are addressed in the General Chapters <731>*Loss on Drying*, <921>*Water Determination*, and <467>*Residual Solvents*.

It should be noted that certain spectroscopic methods suitable for testing of Identity provide simultaneous information about *Water Determination* and *Residual Solvents*. Certain tests are specific to certain herbal materials, such as water-extractable matter, test for bitterness, test for tannins, hemolytic tests for saponins, or some functionality testing such as swelling, foaming, and coloring intensity or coloring power test. Submissions containing these tests must give the rationale and analytical test data in support of suggested specifications.

Additional Requirements

Packaging and Storage

Appropriate packaging and storage statements are defined in the *General Notices* of HMC. Compendial specifications are shelf-life specifications. The proper packaging and storage conditions must be derived and documented from stability studies. The sponsor must provide information about proper container–closure systems and appropriate storage conditions such as temperature and humidity. Under the stated conditions, the Compendial articles are expected to retain the specified standard for the shelf life claimed on the label, certificate of analysis, or equivalent document. Stability studies conducted with the submitted packaging and storage conditions must be provided. Information must be provided as evidence for instability of the herbal material due to exposure to air, light, and moisture. Where no information is received from the submitter, the USP staff will assume the following storage conditions of protection from light, moisture, freezing and excessive heat.

Labeling

As defined in the *HMC General Notices*, labeling includes both the label upon the immediate container and other associated labeling and written, printed, or graphic materials. The label states the Latin binomial name following the authority; the plant part(s), plant product, or processed form contained in the article or from which the article was derived. Content, in percentage, of active principles or marker compounds.

USP Reference Standards

This section lists all authorized Reference Standards needed in order to conduct the monograph tests. Further information about USP Reference Standards is provided in *General Notices* and in the General Chapter <11>*USP Reference Standards*. A list of available official Reference Standards is provided in the USP catalogues and USP website.