

**Monographs in the *Herbal Medicines Compendium*  
Guidelines Document  
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This document provides guidance to sponsors of *Herbal Medicines Compendium (HMC)* monographs of herbal articles used in traditional medicines. Herbal articles, for the purpose of *HMC*, are herbal ingredients in their entire form as well as their processed forms (e.g., powders, extracts, fractions, not including isolated pure compounds) that (1) are approved by a national authority for use as ingredients of herbal traditional medicines, or are included in a national pharmacopeia; and (2) are deemed appropriate for inclusion in the *HMC* by a USP Expert Committee.

### **Monograph categories**

Monograph categories are sections of an *HMC* monograph comprising one or more tests addressing in conjunction a specification for the article. The following information under each monograph category of an *HMC* monograph must be provided for each herbal article. The monograph categories 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 plant part(s) or plant product (e.g., resin, gum-resin), and where 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 author of the Latin binomial will be included under the definition.

#### **Definition**

The following information must 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, leaf, flower, rhizome, etc.), plant product (e.g., resin, gum-resin), and where applicable the processed form. When necessary as dictated and supported by data, the Definition must state the season or period of harvesting for the plant material. When 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 category 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 category usually includes several tests that complement each other. Together, these tests not only serve to ensure the accurate identification of the article, but must be able to distinguish the plant material from related species that may pose potential 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 category are described below.

### ***Macroscopical and Microscopical 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 elements” are 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 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 those materials that would constitute a hazard if inhaled. The words “characteristic odor” may be used to describe the odor characteristic of an herbal article that is considered innocuous.

### ***Chemical Tests***

Analytical methods involving chemical reactions contribute to identification of herbal articles. Chemical tests, such as color tests, that are useful to differentiate the subject species from articles with potential for substitution may be considered. Nonspecific chemical tests must be avoided. Reactions that recognize general classes of compounds such as alkaloids, flavonoids, terpenes, saponins that could produce positive results for similar plant materials must be avoided, unless they provide a means to differentiate potential adulteration due to species substitution.

## **Chromatographic and Other Separation Tests**

Methods involving separation techniques such as thin-layer, liquid, or gas chromatography; capillary electrophoresis; etc. are preferred. Analytical procedures submitted must 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.

### **Fingerprinting**

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 with 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. For 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 materials 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 Reference Plant Material, a reference standard extract, a single chemical entity, or a standardized mixture of substances. Highly

purified single chemical entities are the best reference standards to provide more defined assignation 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 is 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 from 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.

Chemometric approaches may be used to treat the data obtained from the fingerprints of the set and to define the acceptance ranges.

## Composition

Where the chemical entities responsible for a known pharmacological activity for the herbal article are known, *HMC* monographs always include 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 pharmacological 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 marker substance or groups of marker substances. Selection of markers for quantitative

purposes must be made taking in consideration the potential adulteration by the addition of such markers from external sources. 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 the active or marker substance(s) with supportive chromatograms and validation data following the [General Chapter <1225> Validation of Compendial Methods](#). The analytical method, when possible, must be capable of detecting degradants.

## 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 practices, handling, and processing. 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; they arise from the growth of many species of *Aspergillus*, a fungus. 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 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. Also, 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 limit specified in the individual monograph. It is important to achieve selectivity toward toxic metals distinguishing from those that are naturally occurring and have no relevant toxicity at the concentrations typically found in herbal articles (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 the world, and regions and nations differ in this respect. General expectations now in worldwide commerce, as reflected in the World Health Organization (WHO) guidelines, are that when items are imported, the country of origin must be specified.

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 other parts such as twigs and stems. Furthermore, this test is specified to detect adulterants in herbal materials. 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](#). It should be noted that certain spectroscopic methods suitable for testing of Identity (e.g., NMR) provide simultaneous information about *foreign organic matter*.

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* because sand or minerals, or both, are contents of herbals and are a predictable occurrence. 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 water 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 (e.g., NMR) 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: protection from light, moisture, freezing and excessive heat.

It should be noted that certain spectroscopic methods suitable for testing of Identity (e.g., NMR) provide simultaneous information about *stability*.

### **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 and, following the authorized name; 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 may also be stated.

### **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.