Overview of the requirements for homoeopathic products of HERBAL origin

A Guide Through The Different Sections

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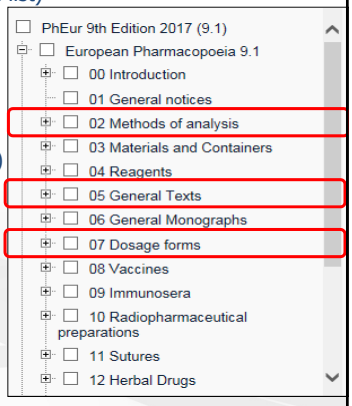
Most important General Chapters for HOM texts (non exhaustive list)

- Foreign matter (2.8.2)
- Water (2.2.13) ; Relative density (2.2.5)
- Gas chromatography (2.2.28) and liquid chromatography (2.2.29)
- Loss on drying (2.2.32) ; Total ash (2.4.16) ; Heavy metals (2.4.27)
- Ash insoluble in hydrochloric acid (2.8.1) ; Swelling index (2.8.4)
- Pesticides (2.8.13)
- Bitterness value (2.8.15) ; Dry residue (2.8.16)
- Aflatoxin B1 (2.8.18), Ochratoxin A (2.8.22)
- Ethanol content (2.9.10) : Methanol and 2-propanol (2.9.11)
- Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use (5.1.4)



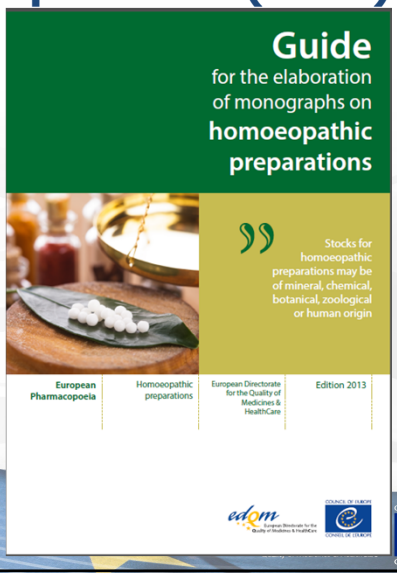
When to require a test for loss on drying (2.2.32) or for water (2.2.13) ?

The Guide for the elaboration of monographs on homoeopathic preparations (2013 Edition) states on page 15:

"*For herbal drugs containing **more than 10 mL/kg (1 per cent) of essential oil**, the determination of water by distillation **(2.2.13)** is carried out instead of the test for loss on drying. The degree of size reduction of the drug or the fineness of the powder using a sieve number (2.1.4) is indicated if required.*"

Guide for the elaboration of monographs on homoeopathic preparations (2013)

https://www.edqm.eu/medias/fichiers/new_guide_for_the_elaboration_of_monographs_on_homoeopathic_preparations_edition_2013.pdf



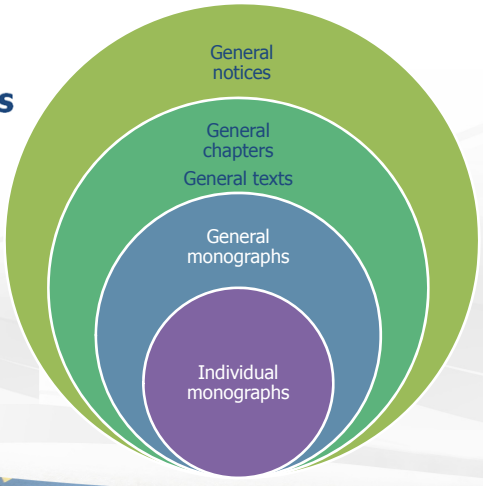
General Monographs (HOM)

General and Specific monographs

ALL APIs, excipients, finished products

Individual monographs → **Relevant General monograph (s)**

COMPLEMENTARITY



Homoeopathic preparations (1038)

DEFINITION: are prepared from substances, products or preparations called stocks, in accordance with a homoeopathic manufacturing procedure

Raw materials: natural or synthetic origin ; TSE and Viral safety (5.1.7)

Ref. Herbal drug PPH (2045)

Vehicles: excipients used for the preparation of certain stocks or for the potentisation process (for ex. purified water, ethanol)

Ref. Mother tincture PPH (2029)

Stocks: starting materials for the production of homoeopathic preparations

Potentisation: usually decimal or centesimal

Dosage form: complies with any relevant dosage form monograph in the European Pharmacopoeia …

Herbal drugs for homoeopathic preparations (2045)

DEFINITION: mainly whole plants or parts of plants, fragmented or broken - include algae, fungi or lichens - usually in fresh form

PRODUCTION: cultivated or wild plants ; suitable collection, cultivation, harvesting, sorting, drying, fragmentation and storage conditions ; free from impurities such as soil, dust, dirt and other contaminants such as fungal, insect and other animal contaminants ; Adequate measures have to be taken in order to ensure the microbiological quality (*5.1.4*)

IDENTIFICATION: macroscopic + where necessary microscopic and others (for example, thin-layer chromatography)

TESTS

ASSAY: where applicable, appropriate method

STORAGE: protected from light.

Mother tinctures for homoeopathic preparations (2029)

DEFINITION: liquid preparations obtained by the solvent action of a suitable vehicle upon raw materials (fresh form but may be dried), from plant juices, with or without the addition of a vehicle

PRODUCTION: maceration, percolation, digestion, infusion, decoction, fermentation or as described in the individual monographs - When contains ethanol, tested for 2-propanol (2.9.11), maximum limit of 0.05 per cent *V/V*

CHARACTERS: appearance, odour

IDENTIFICATION: at least 1 chromatographic Id

TESTS

ASSAY: where applicable, assay with quantitative limits

STORAGE: protected from light, maximum storage temperature.

LABELLING

Herbal drugs for homoeopathic preparations (2045)

TESTS

The tests for foreign matter and loss on drying should be performe

Foreign matter (2.8.2). Where a fresh plant is used as a starting r
maximum content of foreign matter is indicated in the individual mo
Where a dried plant is used as a starting material for the manufact
content of foreign matter is not more than 2 per cent *m/m*, unless o

Adulteration. A specific appropriate test may apply to herbal drug

Loss on drying (2.2.32). Carry out a test for loss on drying on drie
If a fresh plant is processed more than 24 h after harvesting, a test

Water (2.2.13). A determination of water is carried out on herbal d

Pesticides (2.8.13). Herbal drugs for homoeopathic preparations
necessary the preparation in which the plant might be used and, w
performed on the mother tincture according to the requirements of

If appropriate, herbal drugs for homoeopathic preparations comply

Total ash (2.4.16).

Bitterness value (2.8.15).

Heavy metals (2.4.27). Unless otherwise stated in an individual m

- *cadmium*: maximum 1.0 ppm;
- *lead*: maximum 5.0 ppm;
- *mercury*: maximum 0.1 ppm.

If justified by the nature or origin of the herbal drug or if required by
Where justified, the test for heavy metals may be performed on the

Aflatoxin B$_1$ (2.8.18). Where appropriate, limits for aflatoxins may

Ochratoxin A (2.8.22). Where appropriate, a limit for ochratoxin A

Radioactive contamination. In some specific circumstances, the

Mother tinctures for homoeopathic preparations (2029)

TESTS

The limits in an individual monograph are set to include official n

If the test for relative density is carried out, the test for ethanol n

Relative density (2.2.5). The mother tincture for homoeopathic

Ethanol (2.9.10). The ethanol content complies with that prescri

Methanol (2.9.11): maximum 0.05 per cent *V/V*, unless otherw

Dry residue (2.8.16). Where applicable, the mother tincture for

Pesticides (2.8.13). Where applicable, the mother tincture for h

Justification is provided in cases where the test for pesticides is
preparations (2045). Limits are set, taking into consideration the
setting these limits.

Heavy metals (2.4.27). Justification is provided in cases where
drugs for homoeopathic preparations (2045). Limits are set, taki
taken into account when setting these limits.
If required by the competent authority, suitable limits for the con

Aflatoxin B$_1$ (2.8.18). Where appropriate, limits for aflatoxins n
taking into consideration the nature and the origin of the herbal

No cross-reference in individual monographs

Complementarity

- "*General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph, except where a preamble limits the application, for example to substances and preparations that are the subject of a monograph of the pharmacopoeia.*" *General notices*
- "*General monographs and individual monographs are complementary. If the provisions of a general monograph do not apply to a particular product, this is expressly stated in the individual monograph.*" *General notices*
- No cross-reference in individual monographs

➔ *Example: test for foreign matter*

Example: test for foreign matter

Herbal drugs for homoeopathic preparations (2045)

TESTS

The tests for foreign matter and loss on drying should be performed before any further processing of the fresh plant.

Foreign matter (*2.8.2*). Where a fresh plant is used as a starting material for the manufacture of homoeopathic preparations, the content of foreign matter is as low as possible; if necessary, the maximum content of foreign matter is indicated in the individual monograph.

Where a dried plant is used as a starting material for the manufacture of homoeopathic preparations, carry out a test for foreign matter, unless otherwise prescribed in the individual monograph. The content of foreign matter is not more than 2 per cent *m/m*, unless otherwise prescribed or justified and authorised.

Example: test for foreign matter

Hyoscyamus for homoeopathic preparations (2091)

TESTS

Foreign matter (*2.8.2*): if required by the competent authority, maximum 5 per cent

≠ 2 per cent

Ignatia for homoeopathic preparations (2513)

TESTS

CAUTION: when the powdered herbal drug (710) (2.9.12) is used, take the necessary precautions as indicated under Identification B.

Foreign matter (*2.8.2*): maximum 1.0 per cent.

≠ 2 per cent

If the requirement for a specific herbal drug is *maximum 2 per cent* as stated in the general monograph on *Herbal drugs for homoeopathic preparations (2045)*, then **nothing is stated in the individual monograph. The test must nevertheless be done and the limit is 2 per cent.** If the requirement is different, it is stated in the individual monograph.

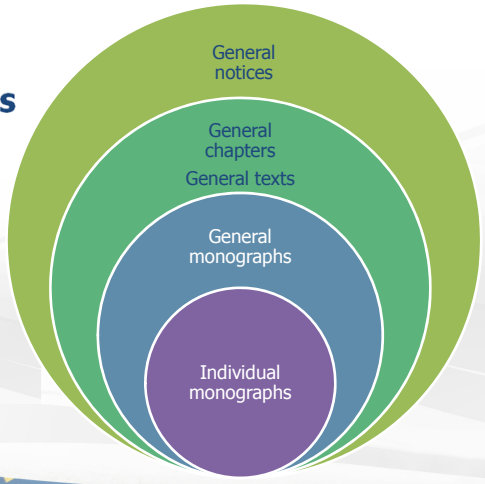
Individual Monographs (HOM)

General and Specific monographs

ALL APIs, excipients, finished products

Individual monographs → **Relevant General monograph (s)**

COMPLEMENTARITY



Individual Herbal monographs

- Title
- Foot note giving the French/English title

- Definition of the herbal drug
- Production (mandatory for manufacturer)

- Potential adulteration (fraudulent activities)
- Characters (for information only)

Individual herbal monographs

- Identification (macroscopic, microscopic, TLC)
- Dried herbal drug → illustration

- Tests (Foreign matter, Loss on drying, adulteration, etc)
- Assay

- Mother tincture part

Individual Herbal monographs

- Definition of the **Mother tincture**
- Production (reference to methods of preparation see *2371*)
- Characters (for information only)

- Identification (chemical reactions, chromatography)
- Tests (relative density, ethanol, methanol, dry residue)
- Assay

- Storage (information and recommendation, but competent authority may make it mandatory)
- Labelling

TITLES & foot note

DEFINITION: defines the scope of the monograph for the herbal drug (a reference to an existing Ph Eur may replace this part), ie the state of the dried herbal drug (whole, fragmented, broken, peeled, dried), the complete scientific name of the plant, the part(s), harvesting time, stage of growth, etc (two different harvesting times may be described as for *Bryonia (2838)*)

IDENTIFICATION A, B, C

EUROPEAN PHARMACOPOEIA 9.0 — 01/2017:2513

IGNATIA FOR HOMOEOPATHIC PREPARATIONS

Strychnos ignatii ad praeparationes homoeopathicas

DEFINITION

Dried, ripe seed of *Strychnos ignatii* P.J.Bergius.

Content: minimum 1.80 per cent for the sum of the contents of brucine ($C_{23}H_{26}N_2O_4$; M_r 394.5) and strychnine ($C_{21}H_{22}N_2O_2$; M_r 334.4), of which minimum 65 per cent consists of strychnine (dried drug).

IDENTIFICATION

A. The seed is grey, brown and dull, up to 3 cm long and 10-25 mm thick. It is irregular, with 3-5 distinct sides: one of these is usually wider, convex and glabrous; the others are angular and flattened and show the remains of testa hairs forming lighter zones in the depressions. The stony granular texture resembles that of pebbles from a river bed; the hilum is found on the most rounded end and forms a small, light brown depression. The fracture shows a compact, semi-translucent, horny endosperm; the embryo is located in the centre and is about 10-15 mm long, with a foliaceous cotyledon.

B. *CAUTION: take all necessary handling precautions when reducing this toxic herbal drug to a powder.*

Wash the herbal drug rapidly in cold water, then expose to steam; once sufficiently softened, cut into thin slices and crush in a suitable apparatus. Allow to dry, finish reducing to a powder (710) (*2.9.12*) and pass through a covered sieve.

Microscopic examination (*2.8.23*). The powder is light brown. Examine under a microscope using *chloral hydrate solution R*. The powder shows the following diagnostic characters (Figure 2513.-1): oil droplets [D]; fragments of endosperm [B, C, F] consisting of thick-walled cells of various sizes, the smallest located at the periphery of the endosperm [Cb] and the largest towards the centre of the seed [F]; a few fragments of the outer layer of the endosperm (surface view [J], transverse section [Ca]), with polygonal cells sometimes associated with the inner layer of the testa, composed of cells with indistinct walls (surface view [E], transverse section [Cd]); sclerified covering trichomes [A, K], sheared off, not enlarged at the base [Aa] and with walls composed of small, oblique, sclerified strips, tightly fused longitudinally [Ab, Ka]; numerous fragments of strips [G, H] and rare rounded tips of covering trichomes [K].

Ignatia for homoeopathic preparations

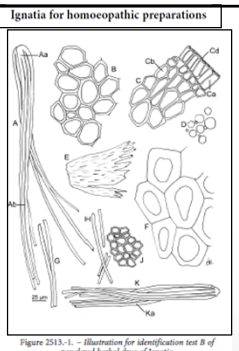


Figure 2513.-1. – *Illustration for identification test B of powdered herbal drug of Ignatia*

C. Thin-layer chromatography (*2.2.27*).

Test solution. To 2.0 g of the powdered herbal drug (710) (*2.9.12*) add 20 ml of *ethanol (70 per cent V/V) R*, allow to macerate for 15 min at room temperature, with stirring, and centrifuge. Use the supernatant.

Reference solution. Dissolve 10 mg of *brucine R* and 10 mg of *strychnine R* in 10 ml of *ethanol (96 per cent) R*.

Plate: TLC silica gel plate R (5-40 µm) [or *TLC silica gel plate R* (2-10 µm)].

Mobile phase: concentrated ammonia R, methanol R, methylene chloride R (1:5:95 *V/V/V*); use the lower layer.

Application: 10 µl [or 5 µl.] as bands.

Development: over a path of 15 cm [or 6 cm].

Drying: in air, then in an oven at 105-110 °C for 15 min; allow to cool.

Detection: spray with *iodoplatinate reagent R* and examine immediately in daylight.

Results: see below the sequence of zones present in the chromatograms obtained with the reference solution and the test solution. Furthermore, other faint zones may be present in the chromatogram obtained with the test solution.

Top of the plate	
Strychnine: a violet zone Brucine: a blue zone	A violet zone (strychnine) A blue zone (brucine)
Reference solution	Test solution

For dried herbal drugs, an illustration is included in the Ph. Eur. Monograph (same for other herbal drugs monographs). Furthermore the statements "(dried drug)" or "(anhydrous drug)" imply that the monograph prescribes respectively a test for loss on drying (2.2.32) or a determination of water by distillation (2.2.13).

Exemple: *Hydrastis canadensis FHP (2500)*: section replaced by a reference to herbal drug monograph *Goldenseal rhizome (1831)*.

TESTS: the tests required by the general monograph *Herbal drugs for homoeopathic preparations (2045)* are not repeated.

In certain cases, additional microscopic examinations and/or additional chemical reactions are carried out. This is done particularly to detect adulteration by drugs that have related morphological appearance but which come from totally different species to demonstrate for example that a given drug is free of toxic substances, such as alkaloids and cardiotonic steroids.

ASSAY: Where necessary, an assay is included.
A chromatogram is shown for information in the knowledge database

Reference standard available from EDQM (see knowledge database)

Reagent: The reagents are described in general chapter 4.

TESTS

CAUTION: when the powdered herbal drug (710) (2.9.12) is used, take the necessary precautions as indicated under Identification B.

Foreign matter (*2.8.2*): maximum 1.0 per cent.

***Strychnos nux-vomica* L.** The presence of flattened discoid seeds and the presence in the powdered herbal drug, examined under a microscope, of testa cells transformed into hairs, with a sclerified base and a lignified tip, bent at a right angle and with 7-10 lignified ridges, and of numerous sclerified rods, indicate adulteration with *Strychnos nux-vomica* L.

Loss on drying (*2.2.32*): maximum 12.0 per cent, determined on 1.00 g of the powdered herbal drug (710) (*2.9.12*) by drying in an oven at 105 °C for 2 h.

Total ash (*2.4.16*): maximum 3.5 per cent.

Aflatoxins (*2.8.18*): maximum 2 µg/kg (aflatoxin B_1) and maximum 4 µg/kg (sum of aflatoxins B_1, B_2, G_1 and G_2).

ASSAY

Liquid chromatography (*2.2.29*).

Test solution. To 1.000 g of the powdered herbal drug (710) (*2.9.12*) add 10.0 ml of *ethanol (60 per cent V/V) R*. Boil gently, with stirring, under a reflux condenser. After 30 min, cool and filter into a 20.0 ml volumetric flask. Wash the filter with *ethanol (60 per cent V/V) R* and dilute to 20.0 ml with the same solvent. Dilute 1.0 ml of the solution to 20.0 ml with mobile phase A.

Reference solution. Dissolve 10.0 mg of *brucine CRS* and 10.0 mg of *strychnine CRS* in *acetonitrile R* and dilute to 10.0 ml with the same solvent. Dilute 1.0 ml of the solution to 20.0 ml with mobile phase A.

Column:

- *size:* l = 0.15 m, Ø = 4.6 mm;
- *stationary phase: ethylene-bridged octadecylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);
- *temperature:* 35 °C.

Mobile phase:

- *mobile phase A: triethylamine R, acetonitrile for chromatography R, methanol R2, tris(hydroxymethyl)aminomethane buffer solution pH 9.0 R* (0.1:7.5:7.5:85 *V/V/V/V*);
- *mobile phase B: triethylamine R, tris(hydroxymethyl)aminomethane buffer solution pH 9.0 R, acetonitrile for chromatography R, methanol R2* (0.1:15:42.5:42.5 *V/V/V/V*);

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 5	100	0
5 - 25	100 → 70	0 → 30
25 - 30	70 → 65	30 → 35
30 - 31	65 → 0	35 → 100
31 - 32	0	100

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 260 nm.

Elution order: brucine, strychnine.

System suitability: reference solution:

- *resolution:* minimum 3.0 between the peaks due to brucine

Calculate the percentage contents of brucine and strychnine using the following expression:

$$\frac{A_1 \times m_2 \times p \times 2}{A_2 \times m_1}$$

A_1 = area of the peak due to brucine or strychnine in the chromatogram obtained with the test solution;
A_2 = area of the peak due to brucine or strychnine in the chromatogram obtained with the reference solution;
m_1 = mass of the herbal drug to be examined used to prepare the test solution, in grams;
m_2 = mass of *brucine CRS* or *strychnine CRS* used to prepare the reference solution, in grams;
P = assigned percentage content of brucine in *brucine CRS* or strychnine in *strychnine CRS*.

Mother tincture

The mother tincture complies with the requirements of the general monograph *Mother tinctures for homoeopathic preparations (2029)*.

DEFINITION

The mother tincture is prepared from the dried, ripe seed of *Strychnos ignatii* P.J.Bergius.

Content: 0.18 per cent *m/m* to 0.36 per cent *m/m* for the sum of the contents of brucine ($C_{23}H_{26}N_2O_4$; M_r 394.5) and strychnine ($C_{21}H_{22}N_2O_2$; M_r 334.4), of which minimum 65 per cent is strychnine.

PRODUCTION

The mother tincture is prepared by the following methods prescribed in the general monograph *Methods of preparation of homoeopathic stocks and potentisation (2371)*:

- method 1.1.8, using the powdered herbal drug (710) (*2.9.12*) and ethanol (70 per cent *V/V*);
- method 1.1.10, using the powdered herbal drug, ethanol (65 per cent *V/V*) and a maceration time of 3-5 weeks.

CHARACTERS

Appearance: brownish yellow liquid.

IDENTIFICATION

Thin-layer chromatography (*2.2.27*) as described in identification test C for the herbal drug with the following modification.

Test solution. The mother tincture to be examined.

TESTS

Relative density (*2.2.5*): 0.890 to 0.904 (method 1.1.8).

Ethanol (*2.9.10*): 60 per cent *V/V* to 70 per cent *V/V* (method 1.1.10).

Dry residue (*2.8.16*): minimum 1.2 per cent.

ASSAY

Liquid chromatography (*2.2.29*) as described in the assay of the herbal drug with the following modification.

Test solution. Dilute 2.000 g of the mother tincture to be examined to 20.0 ml with *ethanol (60 per cent V/V) R*.

Calculate the percentage contents of brucine and strychnine using the following expression:

$$\frac{A_1 \times m_2 \times p}{A_2 \times m_1 \times 10}$$

A_1 = area of the peak due to brucine or strychnine in the chromatogram obtained with the test solution;
A_2 = area of the peak due to brucine or strychnine in the chromatogram obtained with the reference solution;
m_1 = mass of the mother tincture to be examined used to prepare the test solution, in grams;
m_2 = mass of *brucine CRS* or *strychnine CRS* used to prepare the reference solution, in grams;
P = assigned percentage content of brucine in *brucine CRS* or strychnine in *strychnine CRS*.

MOTHER TINCTURE PART

DEFINITION: defines the scope

PRODUCTION
Refer to General Monograph 2371 and includes the production methods used in the Member States

Characters (non mandatory): physical description

IDENTIFICATION: If a TLC test is used both for the control of adulterations and for identification, the method is described entirely under Tests with a cross-reference under Identification.

TESTS: the tests required by the general monograph *Mother tinctures for homoeopathic preparations (2029)* are not repeated.

ASSAY: Where necessary, an assay is included.

01/2017:2029

MOTHER TINCTURES FOR HOMOEOPATHIC PREPARATIONS

STORAGE

Protected from light. A maximum storage temperature may be specified.

LABELLING

The label states:

- that the product is a mother tincture for homoeopathic preparations (designated as 'TM' or 'Ø');
- the name of the raw material using the Latin title of the European Pharmacopoeia monograph where one exists;
- the method of preparation;
- the ethanol content or other solvent content, in per cent *V/V*, in the mother tincture;
- the ratio of raw material to mother tincture;
- where applicable, the storage conditions.

Refer to the General Notices, the relevant General monograph. Additional information may be available in individual monographs.

Storage: The information and recommendations given under the heading Storage do not constitute a pharmacopoeial requirement but the competent authority may specify particular storage conditions that must be met.

The articles described in the Pharmacopoeia are stored in such a way as to **prevent contamination and, as far as possible, deterioration**. Where special conditions of storage are recommended, including the type of container (see section 1.3. General chapters) and limits of temperature, they are stated in the monograph (General Notices).

Labelling: In general, labelling of medicines is subject to supranational and national regulation and to international agreements. The statements under the heading Labelling are not therefore comprehensive and, moreover, for the purposes of the Pharmacopoeia **only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory**. Any other labelling statements are included as recommendations. When the term 'label' is used in the Pharmacopoeia, the labelling statements may appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis accompanying the article, as decided by the competent authority (General Notices).

Example of skip-testing: test for adulteration

Agaricus phalloides for homoeopathic preparations
Amanita phalloides ad prep. homoeopathicas
Ph. Eur. Monograph 2290

TESTS

Other *Amanita* species. Veil remnants on caps are typical for most *Amanita* species, but not for *A. phalloides*. Therefore all mushrooms with veil remnants on the cap have to be discarded. The presence of veil remnants (patches) on the cap indicates adulteration with *A. citrina* (Schaeff.) Pers. (whitish-yellow cap with whitish to brownish patches) or with *A. muscaria* (L.: Fr.) Lamarck, *A. caesarea* (Scop.: Fr.) Pers., or *A. rubescens* Pers. (orange to bright red cap with white patches); a brownish cap indicates adulteration with *A. pantherina* (DC.) Krombh.; a greenish-white cap and a white stipe with a labile annulus indicates adulteration with *A. verna* (Bull.: Fr.) Lamarck.

Ph. Eur. Texts are written for ALL the products on the market. The Competent Autorities are assessing the dossiers for marketing authorisation on a case by case basis.
When a manufacturer can prove to its Competent Authority that none of the other Amanita species can be mixed up with *Amanita phalloides (Vaill. ex Fr.) Link.* (for ex. because such species are not growing in the area of harvest), then the Competent Authority may allow the manufacturer to skip the adulteration test for this particular species.

HOM herbal monographs
Recent developments

- Ph. Eur. 9th Edition *Agaricus phalloides FHP (2290)* (revision assay)

  Ignatia FHP (2513) & Nux-vomica FHP (2514)
  (minor revision to delete ref to sieve in MT production section)

- Ph. Eur. Suppl 9.1 *Homoeopathic preparations (1038)* (minor revision)
- Pharmeuropa 28.3 *Sanguinaria FHP (2687)* (new)
- Pharmeuropa 28.1 *Rhus toxicodendron FHP (2519)* (new)

Thank you for your attention

Questions?

Website: www.edqm.eu