The European Pharmacopoeia (Ph Eur) -

The draft monograph on Cannabis flos published in Pharmeuropa 34.4

Global Workshop on Cannabis Quality - Part one: America & Europe
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Content

- The European Pharmacopoeia

- The draft monograph on Cannabis flos published in Pharmeuropa 34.4
The European Pharmacopoeia (Ph. Eur.)

✓ Lays down common, compulsory quality standards for medicinal products and their constituents in Europe.

✓ Ph. Eur. legally binding -> but monographs regularly revised to reflect state-of-the-art.

The Ph. Eur. network

21 active Groups of experts and 40 working parties (+ 14 “dormant”) elaborating and revising texts, meeting up to 3 times a year, formed of more than 800 experts (mainly from Competent Authorities, Industry, University)

Concerning herbal drugs and herbal drug preparations:

✓ Group 13A
✓ Group 13B
✓ TCM WP
✓ PA WP
General structure of the Ph. Eur.
General notices

At the very beginning of the Ph. Eur.

- address general topics
- aim at providing basic information to the user
- apply to all texts incl. general chapters and texts
- include rules to understand texts, conventional expressions ...

Essential reading before starting to use monographs and other texts
General methods

General methods are referred to in individual or general monographs to become applicable

In herbal drug and herbal drug preparation monographs:

24 general methods published in chapter 2.8 (Methods in pharmacognosy), e.g.:

- Ash insoluble in hydrochloric acid (2.8.1)
- Pesticide residues (2.8.13)
- Test for aristolochic acids in herbal drugs (2.8.21)
- Determination of ochratoxin A in herbal drugs (2.8.22)
- HPTLC of herbal drugs and herbal drug preparations (2.8.25)

In 2021 a new chapter was published:

- Contaminant pyrrolizidine alkaloids (2.8.26)

Other general chapters published in other sections, e.g.:

- Microbiological examination of herbal medicinal products for oral use and extracts used in their preparation (2.6.31)
Monographs


6 general monographs, e.g.:
- Herbal drugs (1433)
- Essential oils (2098)

333 individual monographs, e.g.:
- Aloes cape (0258)
- Aloes dry extract standardised (0259)
- Cassia oil (1496)
- Matricaria liquid extract (1544)
- Rosemary leaf (1560)
- Valerian tincture (1899)
Draft monograph on Cannabis flos published in Pharmeuropa 34.4

https://pharmeuropa.edqm.eu/app/phpa/content/issue34-4/3028E.htm

Deadline: 31/12
**Draft monograph on Cannabis flos: Definition**

**DEFINITION**
Dried, whole or fragmented, fully developed shoot apices of female cultivars of *Cannabis sativa* L.

Content: the measured contents of total tetrahydrocannabinol and total cannabidiol do not deviate each from the values stated on the label by more than ± 10 per cent.

**High THC type:**
- total tetrahydrocannabinol, expressed as Δ⁹-tetrahydrocannabinol (C₂₁H₂₂O₂; M, 314.5): 10.0 per cent to 30.0 per cent (dried drug);
- total cannabidiol, expressed as cannabidiol (C₂₁H₂₂O₂; M, 314.5): maximum 1.0 per cent (dried drug).

**THC/CBD type:**
- total tetrahydrocannabinol, expressed as Δ⁹-tetrahydrocannabinol (C₂₁H₂₂O₂; M, 314.5): 3.0 per cent to 15.0 per cent (dried drug);
- total cannabidiol, expressed as cannabidiol (C₂₁H₂₂O₂; M, 314.5): 3.0 per cent to 15.0 per cent (dried drug).

**High CBD type:**
- total tetrahydrocannabinol, expressed as Δ⁹-tetrahydrocannabinol (C₂₁H₂₂O₂; M, 314.5): maximum 1.0 per cent (dried drug);
- total cannabidiol, expressed as cannabidiol (C₂₁H₂₂O₂; M, 314.5): 5.0 per cent to 20.0 per cent (dried drug).

*Ad-hoc* specifications for content for 3 different types/chemotypes of herbal drug.
PRODUCTION

If the herbal drug is to be prescribed to patients, the shoot apices are cut directly at the base, with minimal stalk remaining.

Statement not applicable for herbal drugs used as raw material for the preparation of extracts
Identification by HPTLC:

Results: see below the sequence of zones present in the chromatograms obtained with reference solution (a) and the test solution. Furthermore, in the chromatogram obtained with the test solution, other very faint zones may be present. If present, the zone due to Δ⁹-tetrahydrocannabinolic acid is more intense than the zone due to Δ⁸-tetrahydrocannabinol. The zone due to cannabidiolic acid is more intense than the zone due to cannabidiol.

<table>
<thead>
<tr>
<th>Top of the plate</th>
<th>Reference solution (a)</th>
<th>Test solution (high THC type)</th>
<th>Test solution (THC/CBD type)</th>
<th>Test solution (high CBD type)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[a] Cannabidiol: a reddish-violet zone</td>
<td></td>
<td></td>
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<tr>
<td>[b] Δ⁹-Tetrahydrocannabinol: a reddish-violet zone</td>
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<tr>
<td>[c] A reddish-violet zone, faint to equivalent (Δ⁹-tetrahydrocannabinol)</td>
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<tr>
<td>[d] A reddish-violet zone, intense (Δ⁹-tetrahydrocannabinolic acid)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>[e] A reddish-violet zone, faint to very faint (cannabidiol)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>[f] A reddish-violet zone, intense (cannabidiolic acid)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[g] A reddish-violet zone, faint (Δ⁸-tetrahydrocannabinol)</td>
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<tr>
<td>[h] A reddish-violet zone (Δ⁸-tetrahydrocannabinolic acid)</td>
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<tr>
<td>[i] A grey to reddish-violet zone, very faint, may be absent (Δ⁸-tetrahydrocannabinol)</td>
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<tr>
<td>[j] A reddish-violet zone, very faint (cannabidiol)</td>
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<tr>
<td>[k] A reddish-violet zone, intense (cannabidiolic acid)</td>
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<tr>
<td>[l] A grey to reddish-violet zone, very faint (cannabidiol)</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Test for Total CBN (i.e. CBN + CBNA) (1/4)

Test solution (a): 5mg/mL solution of the herbal drug (HD) used for the Test for total CBN
• Test solution (b): 0.5 mg/mL solution of the herbal drug (HD) used for the Assay

Reference solution (a): contains cannabidiol for cannabis CRS used for quantification.
• Reference solution (b): 1% CBD solution relative to the concentration of the HD in test solution (a) used for the Test for total CBN
• Reference solution (c): 14.4% CBD solution relative to the concentration of the HD in test solution (b) used for the Assay

↑Quantitation at one concentration point↑

Reference solution (d): contains cannabis flower for system suitability HRS, used for peak identification and system suitability for the Test for total CBN
• Reference solution (e): used for peak identification and system suitability for the Assay

Selectivity checked including 17 cannabinoids.
Draft monograph on Cannabis flos: Tests (2/5)

Test for Total CBN (i.e. CBN + CBNA) (2/4)

Chromatographic conditions

**Column:**
- size: $l = 0.15$ m, $\varnothing = 4.6$ mm;
- stationary phase: end-capped solid core polar-embedded octadecylsilyl silica gel for chromatography R (2.7 $\mu$m);
- temperature: 35 °C.

**Mobile phase:** 0.1 per cent V/V solution of trifluoroacetic acid $R$, acetonitrile for chromatography $R$ (41:59 V/V).

**Flow rate:** 2.0 mL/min.

**Detection:** spectrophotometer at 228 nm.

**Injection:** 5 $\mu$L of test solution (a) and reference solutions (b) and (d).

(5) Cortos Shield RP18 is suitable.

Instructions for peak identification

**Identification of peaks:** use the chromatogram obtained with reference solution (b) to identify the peak due to cannabidiol; use the chromatogram supplied with cannabis fower for system suitability HRS and the chromatogram obtained with reference solution (d) to identify the peaks due to $\Delta^1$-tetrahydrocannabinol, $\Delta^8$-tetrahydrocannabinolic acid, cannabidiolic acid, cannabinol, cannabinoic acid, cannabichromene, cannabigerol and cannabigerolic acid.

**Relative retention** with reference to cannabidiol (retention time = about 6.9 min): cannabidiolic acid = about 1.10; cannabigerol = about 1.17; cannabinol = about 1.48; cannabigerolic acid = about 1.63; $\Delta^8$-tetrahydrocannabinol = about 1.76; cannabinoic acid = about 2.38; cannabichromene = about 2.48; $\Delta^8$-tetrahydrocannabinolic acid = about 2.78.
Draft monograph on Cannabis flos: Tests (3/5)

Test for Total CBN (i.e. CBN + CBNA) (3/4)

System suitability test containing three acceptance criteria

- **Minimum 2.5 p/v ratio between CBG & CBDA**
- **Minimum 2.0 Rs between CBGA & \(\Delta^9\)-THC**
- **Minimum 5.0 p/v ratio between CBNA & CBC**
Draft monograph on Cannabis flos: Tests (4/5)

Test for Total CBN (i.e. CBN + CBNA) (4/4)

Calculate the percentage content of total CBN, using the following expression:

\[
\frac{(A_1 \times 0.4) + (A_2 \times 0.9 \times 0.876)}{A_2 \times m_1 \times 4} \times m_1 \times p
\]

- **$A_1$** = area of the peak due to cannabinol in the chromatogram obtained with test solution (a);
- **$A_2$** = area of the peak due to cannabidiol in the chromatogram obtained with reference solution (b);
- **$A_3$** = area of the peak due to cannabinoic acid in the chromatogram obtained with test solution (a);
- **$m_1$** = mass of the herbal drug to be examined used to prepare test solution (a), in grams;
- **$m_2$** = mass of cannabidiol for cannabis CRS used to prepare reference solution (a), in grams;
- **$p$** = percentage content of cannabidiol in cannabidiol for cannabis CRS;
- **0.4** = correction factor of cannabinol with reference to cannabidiol;
- **0.9** = correction factor of cannabinoic acid with reference to cannabidiol;
- **0.876** = ratio of the molecular mass of cannabinoic acid to that of cannabidiol.

**Limit:**
- **total CBN**: maximum 1.0 per cent.

**Total CBN = CBN + CBNA (as CBN)**
Draft monograph on Cannabis flos: Tests (5/5)

Test for Foreign matter

Foreign matter (2.8.2): maximum 2 per cent, if the herbal drug is to be prescribed to patients, it does not contain any seeds and the whole herbal drug does not contain any leaves more than 1.0 cm in length.

Carry out the determination using 25-50 g.

Requirements: not applicable for herbal drugs used as raw material for the preparation of extracts.

Test for Loss on drying

Loss on drying (2.2.32): maximum 10.0 per cent, determined on 1.000 g of the milled(1) herbal drug (not sieved) by drying in vacuo at 40 °C for 24 h.

(1) Mill all samples according to an appropriate procedure.

Tests for Elemental impurities

Arsenic (2.4.27): maximum 0.2 ppm.
Cadmium (2.4.27): maximum 0.3 ppm.
Lead (2.4.27): maximum 0.5 ppm.
Mercury (2.4.27): maximum 0.1 ppm.
Liquid chromatography (2.2.29) as described in the test for total CBN, with the following modifications.

Injection: test solution (b) and reference solutions (c) and (e).

System suitability: reference solution (e):

- resolution: minimum 2.0 between the peaks due to cannabidiol and cannabidiolic acid.

SST: min 2.0 Rs between CBD & CBDA
Draft monograph on Cannabis flos: Assay (2/2)

Total tetrahydrocannabinol = $\Delta^9$-THC + $\Delta^9$-THCA (as $\Delta^9$-THC)
Total cannabidiol = CBD + CBDA (as CBD)
The first sentence of the LABELLING section is necessary in order to assess the specification for content regarding the maximum ± 10 per cent allowed deviation.

The second sentence of the LABELLING section is necessary in order to fully assess the statement of the PRODUCTION section and the requirements of the test for Foreign matter.
Draft monograph on Cannabis flos: pertinent general monographs

The draft is to be read in conjunction with general monograph *Herbal drugs (1433)*, which includes additional requirements that are applicable unless otherwise stated in the draft. For example:

**Pesticides (2.8.13).** Dried herbal drugs comply with the requirements for pesticide residues. The requirements take into account the nature of the plant, where necessary the preparation in which the plant might be used, and where available the knowledge of the complete treatment record of the batch of the plant.

**Microbial contamination.** Where a dried herbal drug is used whole, cut or powdered as an ingredient in a medicinal product, the microbial contamination is controlled (5.1.8. Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation or 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use (e.g. for cutaneous use)).
Draft monograph on Cannabis flos: pertinent general chapters

Moreover, the draft is to be read in conjunction with pertinent general chapters referred to in the draft itself. For example:

**Foreign matter (2.8.2):** maximum 2 per cent; if the herbal drug is to be prescribed to patients, it does not contain any seeds and the whole herbal drug does not contain any leaves more than 1.0 cm in length.

2.8.2. FOREIGN MATTER

Foreign matter is material consisting of any or all of the following:

1) **foreign organs**: matter coming from the source plant but not defined as the herbal drug;

2) **foreign elements**: matter not coming from the source plant and of either vegetable or mineral origin;

3) **other foreign elements**: matter such as moulds and animal contamination (e.g. insects, their eggs or larvae, spiders, rodents and excreta) and any other unwanted matter (e.g. glass, metal, plastics).

The quantitative limits for foreign matter that are specified in the general monographs *Herbal drugs (1433)* or *Herbal drugs for homoeopathic preparations (2045)* or in an individual monograph, as appropriate, only apply to 'foreign organs' and 'foreign elements'; 'other foreign elements' as defined under 3 are not covered by the limit but should, as far as possible, be absent.
A Ph. Eur. monograph is not a stand-alone text and must be read in conjunction with the General Notices, pertinent general texts and applicable general monographs.
Join us in paving the way for the future...

Contribute to the protection of public health by:

- Making your comments count !!!
- Being part of a dynamic scientific community !!!

Deadline for comments on Pharmeuropa 34.4: 31/12
Thank you for your attention

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