THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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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

7th December 2022

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Content

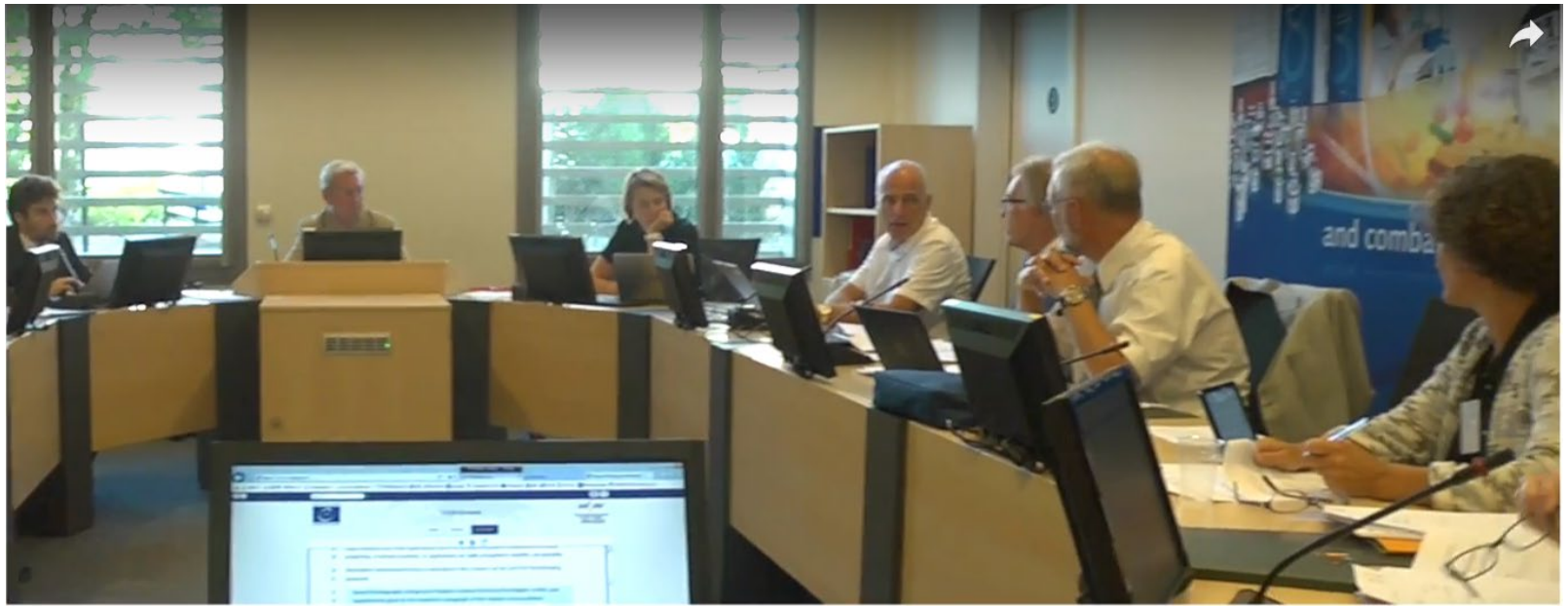
- The European Pharmacopoeia
- The draft monograph on Cannabis flos published in Pharmeuropa 34.4

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.
- ✓ Mandatory on the same date in 39 member states and the European Union (EU) (EU Directive 2001/83/EC as amended, on medicines for human use and EU Regulation 2019/6 on veterinary medicinal products).

The Ph. Eur. network

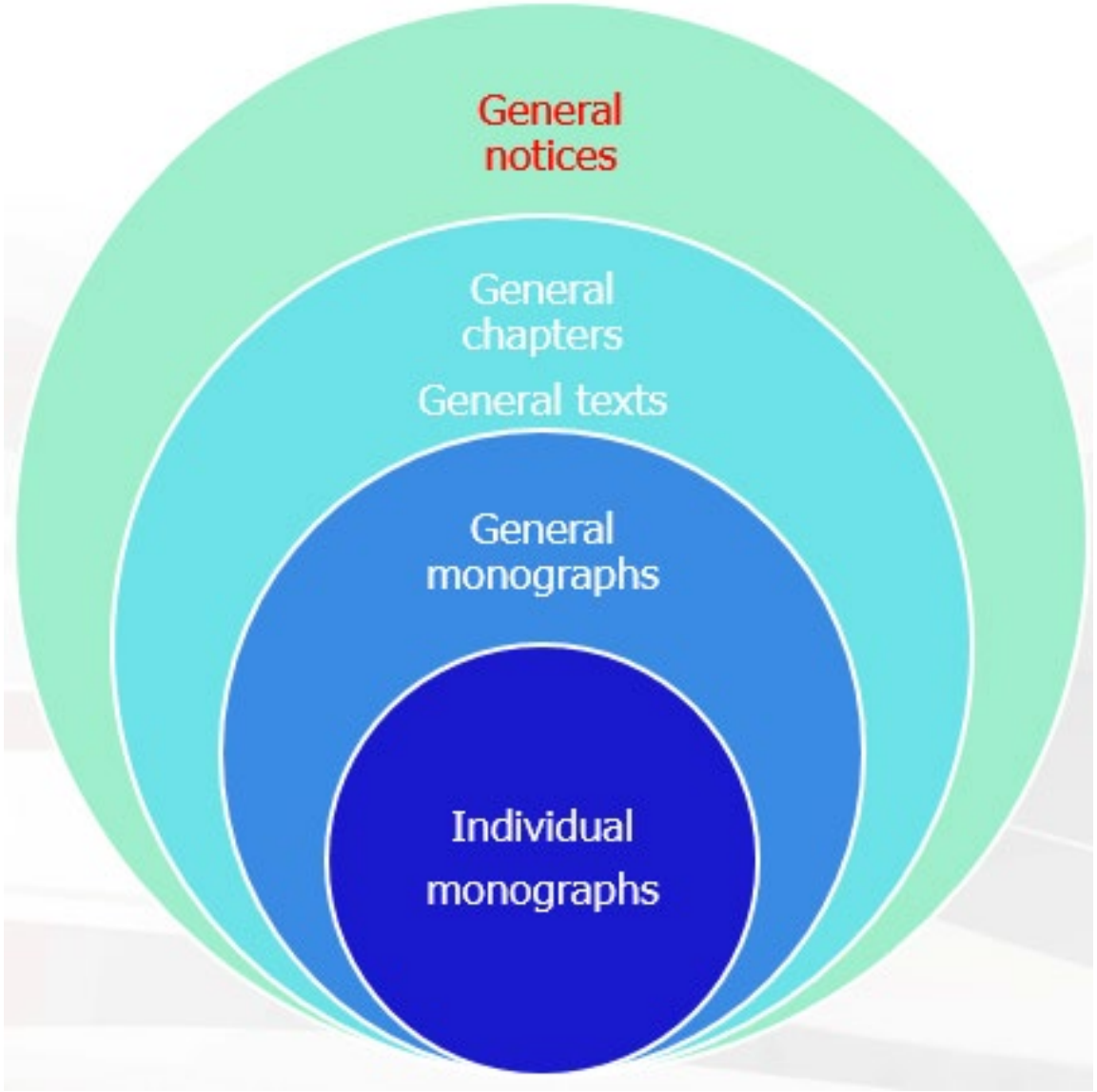
21 active Groups of experts and **40 working parties** (+ 14 "dormant") elaborating and revising texts, meeting up to 3 times a year, formed of more than 800 experts (mainly from Competent Authorities, Industry, University)



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


COUNCIL OF EUROPE
CONSEIL DE L'EUROPE
EUROPEAN PHARMACOPOEIA 11.0
HOME 10TH EDITION 11TH EDITION ARCHIVES
Document en Français
PDF
Knowledge Database
General Notices apply to all monographs and other texts.
See the information section on general monographs.
HERBAL DRUGS
Plantae medicinales
DEFINITION
Herbal drugs are mainly whole, fragmented or broken plants or parts of plants in an unprocessed state, usually in dried form
the word 'plant' is used in the broader sense to also include algae, fungi and lichens. Certain exudates that have not been sul
to be herbal drugs. Herbal drugs are precisely defined by the botanical scientific name according to the binominal system (ge
Whole describes a herbal drug that has not been reduced in size and is presented, dried or undried, as harvested; for examp
chamomile flower.
Fragmented describes a herbal drug that has been reduced in size after harvesting to permit ease of handling, drying and/or
passion flower.
Broken describes a herbal drug in which the more-fragile parts of the plant have broken during drying, packaging or transpor
flower, hop strobile.
Cut describes a herbal drug that has been reduced in size, other than by powdering, to the extent that the macroscopic descr
longer be applied. When a herbal drug is cut for a specific purpose that results in the cut herbal drug being homogeneous, fo
drug preparation. Certain cut herbal drugs processed in this way may be the subject of an individual monograph.
A herbal drug that complies with its monograph and is subsequently cut for extraction shall comply in its cut form, except for
for that herbal drug, unless otherwise justified.
The term *herbal drug* is synonymous with the term *herbal substance* used in European Community legislation on herbal medi
DRIED HERBAL DRUGS

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

Monographs on Herbal drugs and herbal drug preparations

in European Pharmacopoeia 11th Edition 2022 (11.1):

6 general monographs, e.g.:

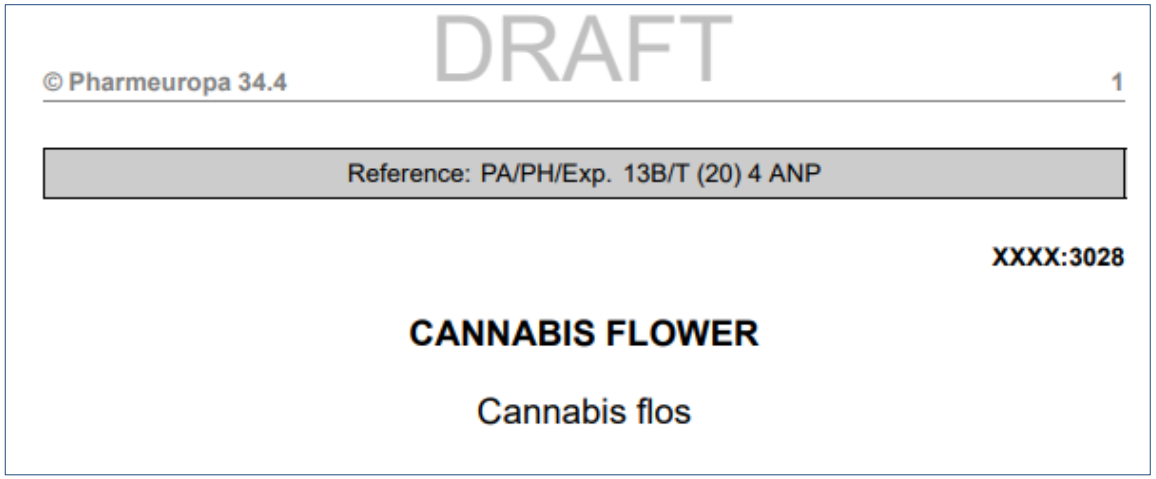
✓Herbal drugs (1433)
✓Essential oils (2098)

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://www.edqm.eu/en/-/ph.-eur.-publishes-cannabis-flos-draft-monograph-in-pharmeuropa-for-comment



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

Draft monograph on Cannabis flos: Definition

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

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 Δ^9-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): 10.0 per cent to 30.0 per cent (dried drug);

– *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): maximum 1.0 per cent (dried drug).

THC/CBD type:

– *total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): 3.0 per cent to 15.0 per cent (dried drug);

– *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): 3.0 per cent to 15.0 per cent (dried drug).

High CBD type:

– *total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): maximum 1.0 per cent (dried drug);

– *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): 5.0 per cent to 20.0 per cent (dried drug).

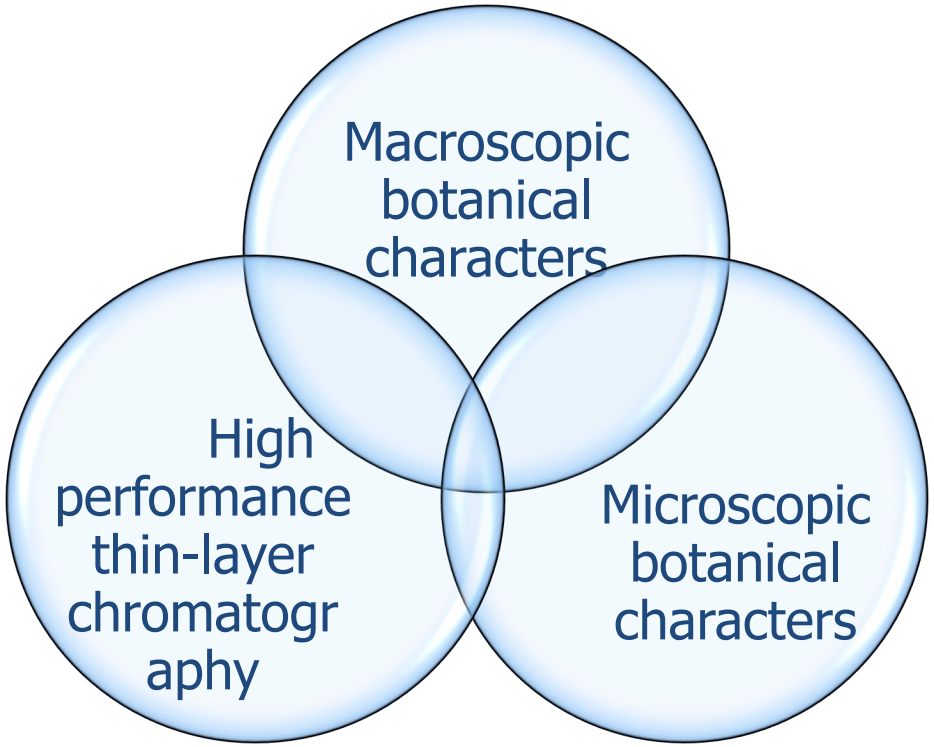
Draft monograph on Cannabis flos: Production

PRODUCTION

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

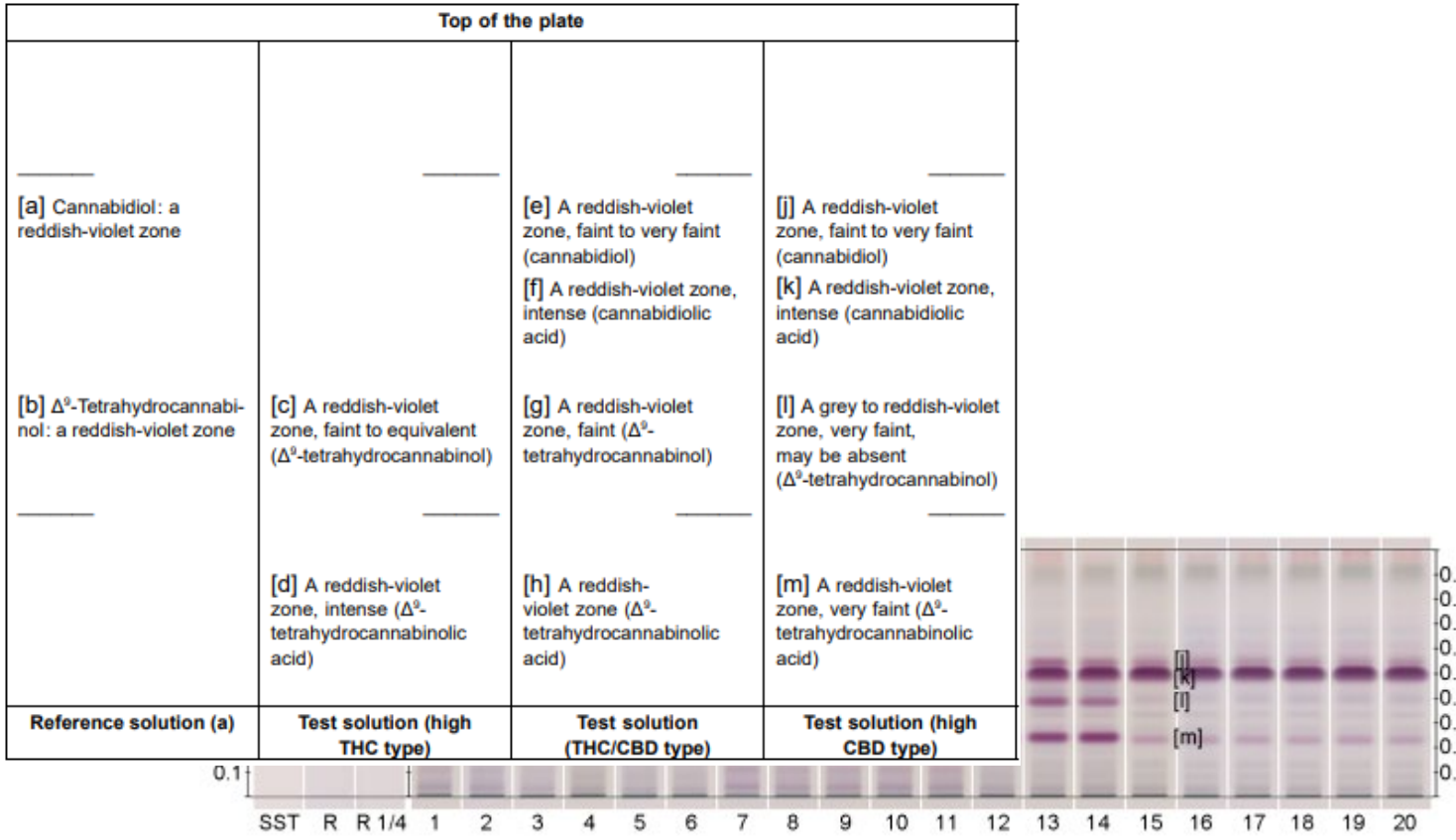
Statement not applicable for herbal drugs used as raw material for the preparation of extracts

Draft monograph on Cannabis flos: Identification



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[3]. If present, the zone due to Δ^9-tetrahydrocannabinolic acid is more intense than the zone due to Δ^9-tetrahydrocannabinol. The zone due to cannabidiolic acid is more intense than the zone due to cannabidiol.



Draft monograph on Cannabis flos: Tests (1/5)

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**

Total CBN. Liquid chromatography (*2.2.29*).

Test solution (a). To 0.50 g of the milled[(1)] herbal drug (not sieved) in a suitable centrifuge tube fitted with a screw cap, add 40 mL of *ethanol (96 per cent) R* and shake for 15 min at about 400 r/min. Centrifuge at about 1700 *g* and transfer the clear supernatant into a flask. Repeat the extraction twice with 25 mL of *ethanol (96 per cent) R*. Combine the supernatants and dilute to 100.0 mL with *ethanol (96 per cent) R*. Filter through a membrane filter (nominal pore size 0.45 µm)[(4)].

Test solution (b). Dilute 1.0 mL of test solution (a) to 10.0 mL with *methanol R*.

Reference solution (a). Dissolve 20.0 mg of *cannabidiol for cannabis CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dilute 5.0 mL of reference solution (a) to 20.0 mL with *methanol R*.

Reference solution (c). Dilute 9.0 mL of reference solution (a) to 25.0 mL with *methanol R*.

Reference solution (d). To 50 mg of milled[(1)] *cannabis flower for system suitability HRS* (not sieved) in a suitable centrifuge tube fitted with a screw cap, add 4 mL of *ethanol (96 per cent) R* and shake for 15 min at about 400 r/min. Centrifuge the solution at about 1700 *g* and transfer the clear supernatant into a flask. Repeat the extraction twice with 2.5 mL of *ethanol (96 per cent) R*. Combine the supernatants and dilute to 10 mL with *ethanol (96 per cent) R*. Filter through a membrane filter (nominal pore size 0.45 µm)[(4)].

Reference solution (e). Dilute 1 mL of reference solution (d) to 10 mL with *methanol R*.

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

(4) PTFE filter Rotilabo®-Spritzenfilter (Order-No.: PP46.1) from Carl Roth is suitable.

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, Ø = 4.6 mm;

– *stationary phase*: *end-capped solid core polar-embedded octadecylsilyl silica gel for chromatography R* (2.7 µm)(5);

– *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 µL of test solution (a) and reference solutions (b) and (d).

(5) Cortecs 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 flower for system suitability HRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to Δ^9-tetrahydrocannabinol, Δ^9-tetrahydrocannabinolic acid, cannabidiolic acid, cannabinol, cannabinolic 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; Δ^9-tetrahydrocannabinol = about 1.76; cannabinolic acid = about 2.38; cannabichromene = about 2.48; Δ^9-tetrahydrocannabinolic acid = about 2.78.

Draft monograph on Cannabis flos: Tests (3/5)

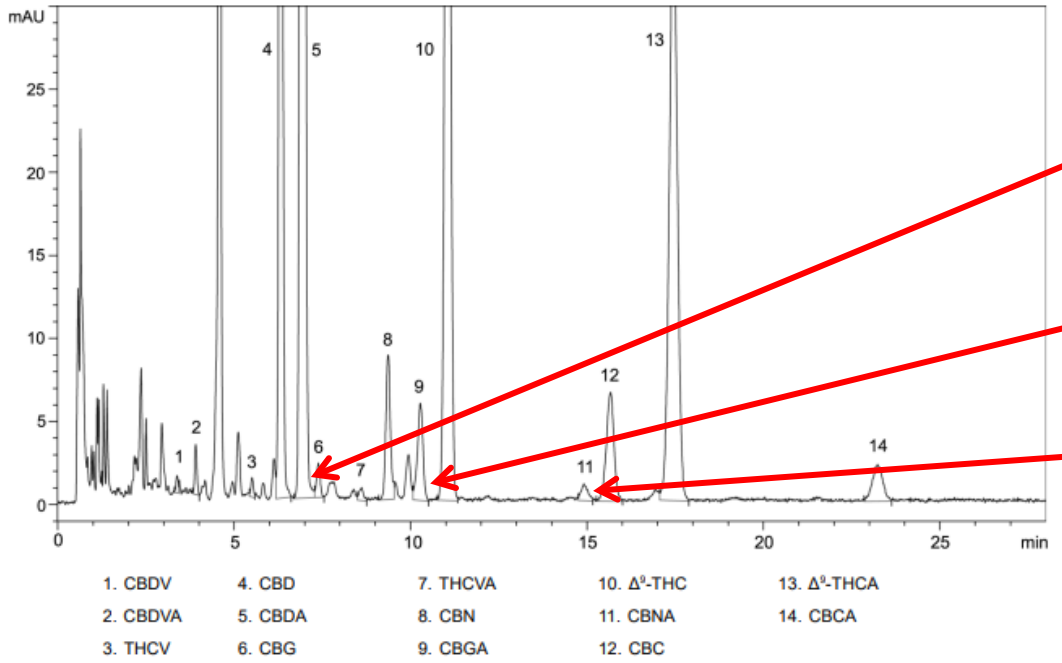
Test for Total CBN (i.e. CBN + CBNA) (3/4)

System suitability test containing three acceptance criteria

System suitability: reference solution (d):

- *resolution*: minimum 2.0 between the peaks due to cannabigerolic acid and Δ^9-tetrahydrocannabinol;
- *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to cannabigerol and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to cannabidiolic acid; minimum 5.0, where H_p = height above the baseline of the peak due to cannabinolic acid and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to cannabichromene.

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.



1. CBDV
2. CBDVA
3. THCV
4. CBD
5. CBDA
6. CBG
7. THCVA
8. CBN
9. CBGA
10. Δ^9-THC
11. CBNA
12. CBC
13. Δ^9-THCA
14. CBCA

Figure 3028.-9. – *Chromatogram for the test for total CBN of cannabis flower: test solution (a) of THC/CBD type*

min 2.5 p/v ratio between CBG & CBDA

min 2.0 Rs between CBGA & Δ^9-THC

min 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)

Quantitation

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

$$\frac{((A_1 \times 0.4) + (A_3 \times 0.9 \times 0.876)) \times m_2 \times p}{A_2 \times m_1 \times 4}$$

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 cannabinolic 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 cannabinolic acid with reference to cannabidiol;
0.876	=	ratio of the molecular mass of cannabinol to that of cannabinolic acid.

Specification

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.

Requirement not applicable for herbal drugs used as raw material for the preparation of extracts

Carry out the determination using 25-50 g.

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.

Draft monograph on Cannabis flos: Assay (1/2)

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

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.

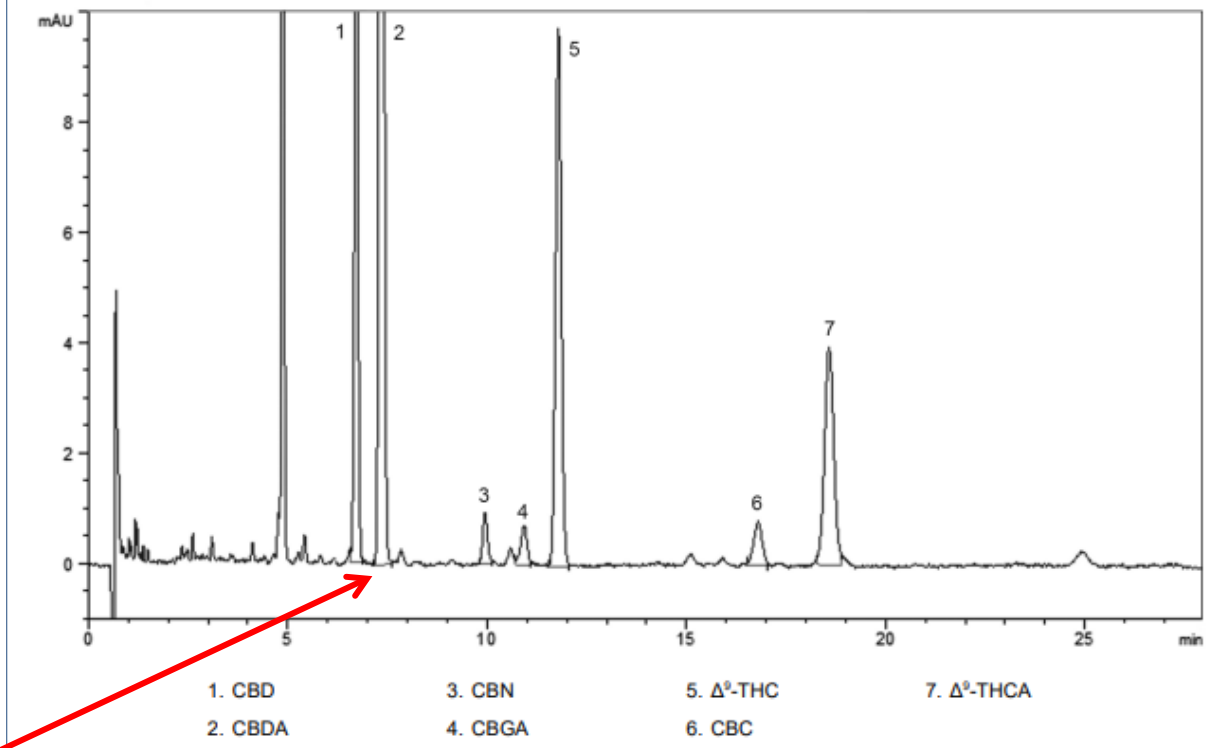


Figure 3028.-16. – *Chromatogram for the assay of cannabis flower: test solution (b) of THC/CBD type*

Draft monograph on Cannabis flos: Assay (2/2)

Calculate the percentage content of total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol, using the following expression:

$$\frac{((A_1 \times 1.08) + (A_3 \times 0.67 \times 0.877)) \times m_2 \times p \times 3.6}{A_2 \times m_1}$$

A_1	=	area of the peak due to Δ^9-tetrahydrocannabinol in the chromatogram obtained with test solution (b);
A_2	=	area of the peak due to cannabidiol in the chromatogram obtained with reference solution (c);
A_3	=	area of the peak due to Δ^9-tetrahydrocannabinolic acid in the chromatogram obtained with test solution (b);
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*;
1.08	=	correction factor of Δ^9-tetrahydrocannabinol with reference to cannabidiol;
0.67	=	correction factor of Δ^9-tetrahydrocannabinolic acid with reference to cannabidiol;
0.877	=	ratio of the molecular mass of Δ^9-tetrahydrocannabinol to that of Δ^9-tetrahydrocannabinolic acid.

Calculate the percentage content of total cannabidiol, expressed as cannabidiol, using the following expression:

$$\frac{(A_1 + (A_3 \times 0.58 \times 0.877)) \times m_2 \times p \times 3.6}{A_2 \times m_1}$$

A_1	=	area of the peak due to cannabidiol in the chromatogram obtained with test solution (b);
A_2	=	area of the peak due to cannabidiol in the chromatogram obtained with reference solution (c);
A_3	=	area of the peak due to cannabidiolic acid in the chromatogram obtained with test solution (b);
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*;
0.58	=	correction factor of cannabidiolic acid with reference to cannabidiol;
0.877	=	ratio of the molecular mass of cannabidiol to that of cannabidiolic acid.

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 Δ^9-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): 10.0 per cent to 30.0 per cent (dried drug);
- *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): maximum 1.0 per cent (dried drug).

THC/CBD type:

- *total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): 3.0 per cent to 15.0 per cent (dried drug);
- *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): 3.0 per cent to 15.0 per cent (dried drug).

High CBD type:

- *total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): maximum 1.0 per cent (dried drug);
- *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): 5.0 per cent to 20.0 per cent (dried drug).

Total tetrahydrocannabinol = Δ^9-THC + Δ^9-THCA (as Δ^9-THC)
Total cannabidiol = CBD + CBDA (as CBD)

Draft monograph on Cannabis flos: Storage & Labelling

STORAGE

In an airtight container.

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.

The first sentence of the LABELLING section is necessary in order to asses the specification for content regarding the maximum ± 10 per cent allowed deviation

LABELLING

The label states the percentage contents of total tetrahydrocannabinol and total cannabidiol.

In addition, the label states if the herbal drug is to be prescribed to patients.

The second sentence of the LABELLING section is necessary in order to fully asses the statement of the PRODUCTION section and the requirements of the test for Foreign matter

PRODUCTION

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

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.

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:

07/2017:1433

HERBAL DRUGS

Plantae medicinales

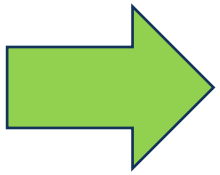
Pesticides (*2.8.13*). Dried herbal drugs comply with the requirements for pesticide residues. The requirements take into account the nature of the plant, where necessary the preparation in which the plant might be used, and where available the knowledge of the complete treatment record of the batch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



04/2023:20802

2.8.2. FOREIGN MATTER

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

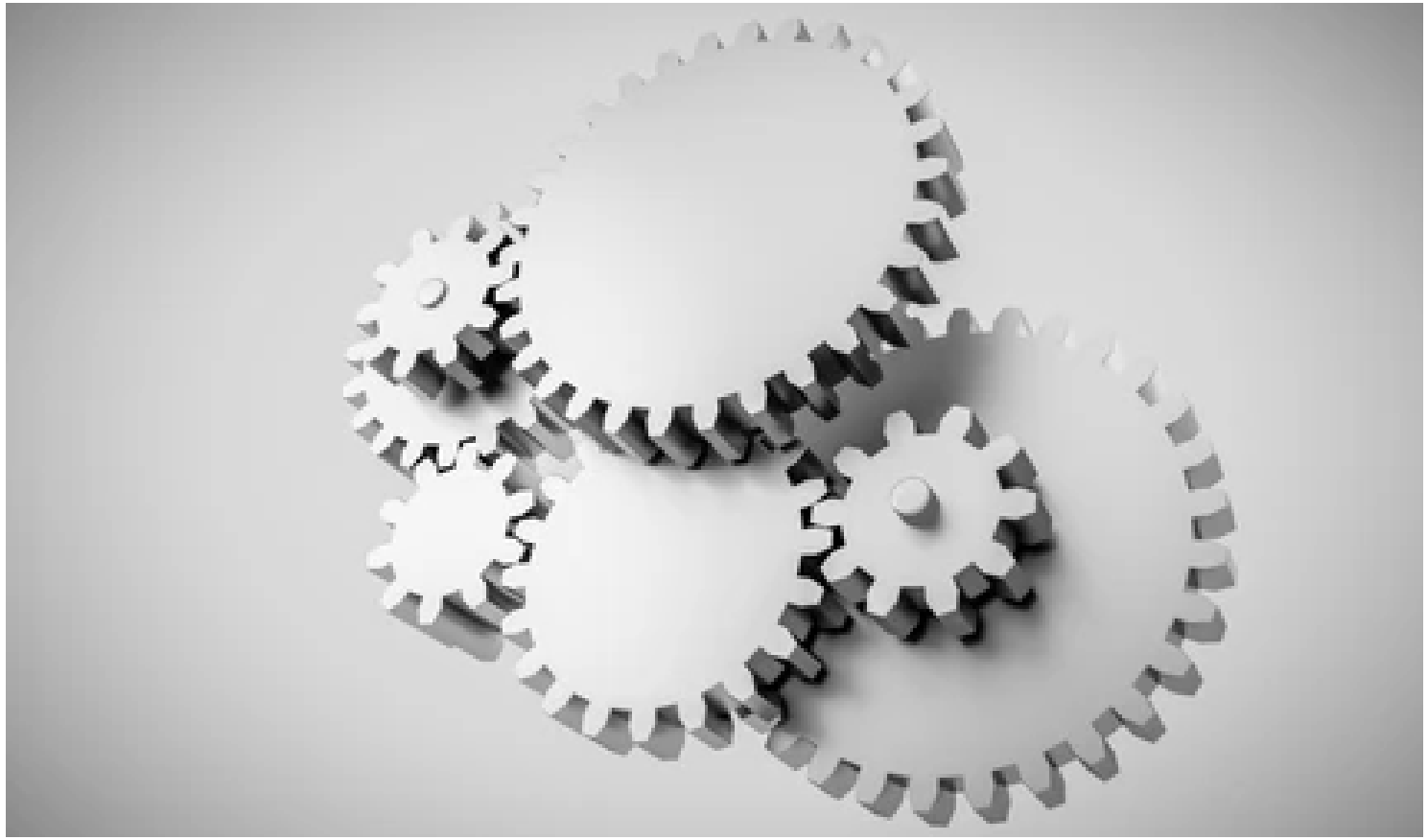
1) *foreign organs*: matter coming from the source plant but not defined as the herbal drug;

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



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Contribute to the protection of public health by:

- Making your comments count !!!

PHARMEUROPA ONLINE

TEXTS FOR COMMENT

ACCESS

Deadline for comments on Pharmeuropa 34.4: 31/12

- Being part of a dynamic scientific community !!!

JOIN THE NETWORK!

Thank you for your attention

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