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

edqm

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

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

The *European Pharmacopoeia* (*Ph. Eur.*) - The new *Ph. Eur.* monograph on *Cannabis flower* (3028)

EDQM webinar

Online: 14 December 2023 15:30 – 17:00 (CET, France)

Dr. Jaume SANZ-BISET

Scientific Programme Officer, European Pharmacopoeia Department, European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe

Content

- The *European Pharmacopoeia* (*Ph. Eur.*)
- *Ph. Eur.* monographs on herbal drugs
- The new *Ph. Eur.* monograph on *Cannabis flower (3028)*
- Final remarks

The EDQM, a Directorate of the COUNCIL OF EUROPE

COUNCIL OF EUROPE

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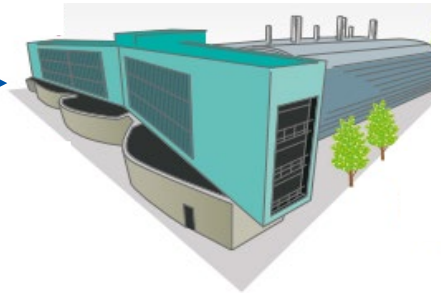
COMMITTEE OF MINISTERS | PARLIAMENTARY ASSEMBLY | CONGRESS OF LOCAL AND REGIONAL AUTHORITIES | EUROPEAN COURT OF HUMAN RIGHTS | COMMISSIONER OF HUMAN RIGHTS | CONFERENCE OF INGOS

- Founded in **1949**
- **Intergovernmental** organisation, Strasbourg
- **46** Member States
- More than **700 Million** of Citizens

Council of Europe is not the European Union!

The **European Directorate for the Quality of Medicines and HealthCare** (EDQM)



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

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

- Founded in 1964
- Work in the framework of a **Partial Agreement, 39 Members & the EU**
- Contribute to **Public Health and access to good quality medicines and healthcare in Europe**

European Pharmacopoeia

- 11th Edition contains **2469 monographs (including dosage forms), 386 general texts** (including general monographs and methods of analysis) and more than **2800 descriptions of reagents**.

- Protecting public health – one common compulsory standard
- Applied by all licencing authorities
- Legally binding quality standards for all medicinal products
- Mandatory on the same date for all member states

39 member states and the EU
33 Observers (31 countries, TFDA and WHO)

European Pharmacopoeia Commission

European Pharmacopoeia Commission

Composed of :

- 39 member states
- European Union
- 33 Observers:
  - 5 European countries
  - 26 non-European countries
  - Taiwan Food and Drug Administration (TFDA)
  - World Health Organization (WHO)

Presidium

- Chair
- 2 Vice-chairs
- Ph. Eur. Secretariat

Presidium Meetings + Meeting of Chairs of Groups of Experts

Groups of experts

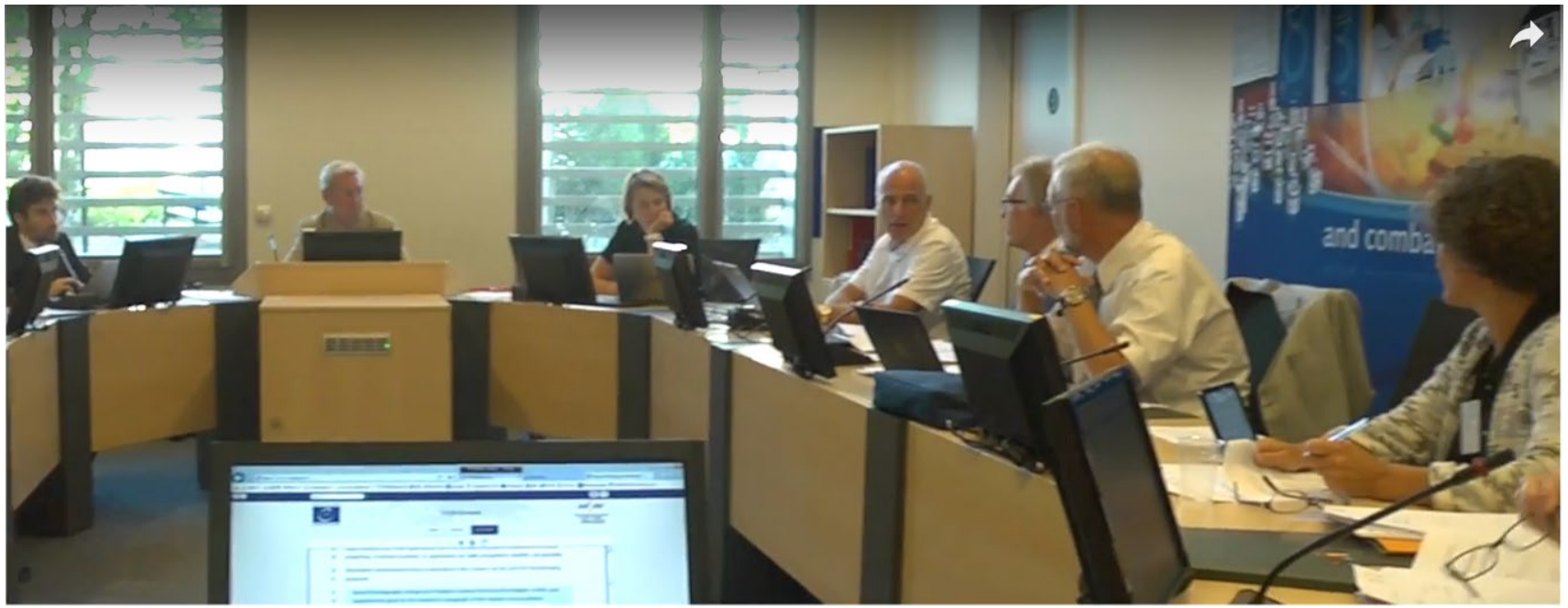
Working parties

- ✓ One delegation per member state / Observer
- ✓ Three sessions a year
- ✓ Texts are adopted by unanimous vote
- ✓ Composition of groups of experts decided by Ph. Eur. Commission

The *European Pharmacopoeia (Ph. Eur.)*

The Ph. Eur. network of experts

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 900 experts (mainly from Competent Authorities, Industry, University)

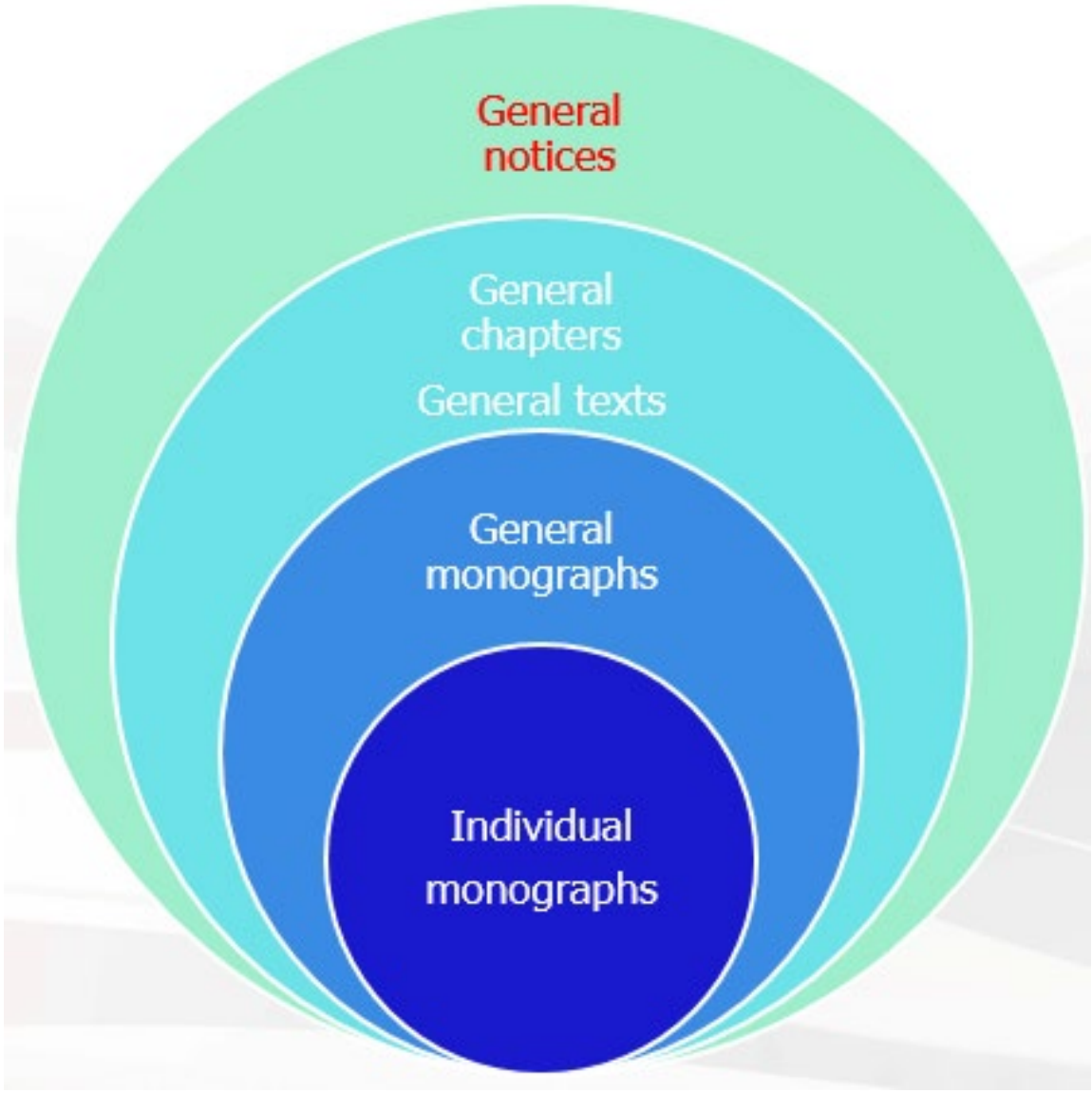


Concerning herbal drugs and herbal drug preparations:

- ✓ Group 13A
- ✓ Group 13B
- ✓ TCM WP
- ✓ PA WP

The *European Pharmacopoeia* (*Ph. Eur.*)

General structure of the Ph. Eur.



The *European Pharmacopoeia (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

The *European Pharmacopoeia* (*Ph. Eur.*)

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)

✓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)

The *European Pharmacopoeia* (*Ph. Eur.*)

Monographs on Herbal drugs and herbal drug preparations in European Pharmacopoeia 11th Edition 2022 (11.4):

6 general monographs, e.g.:

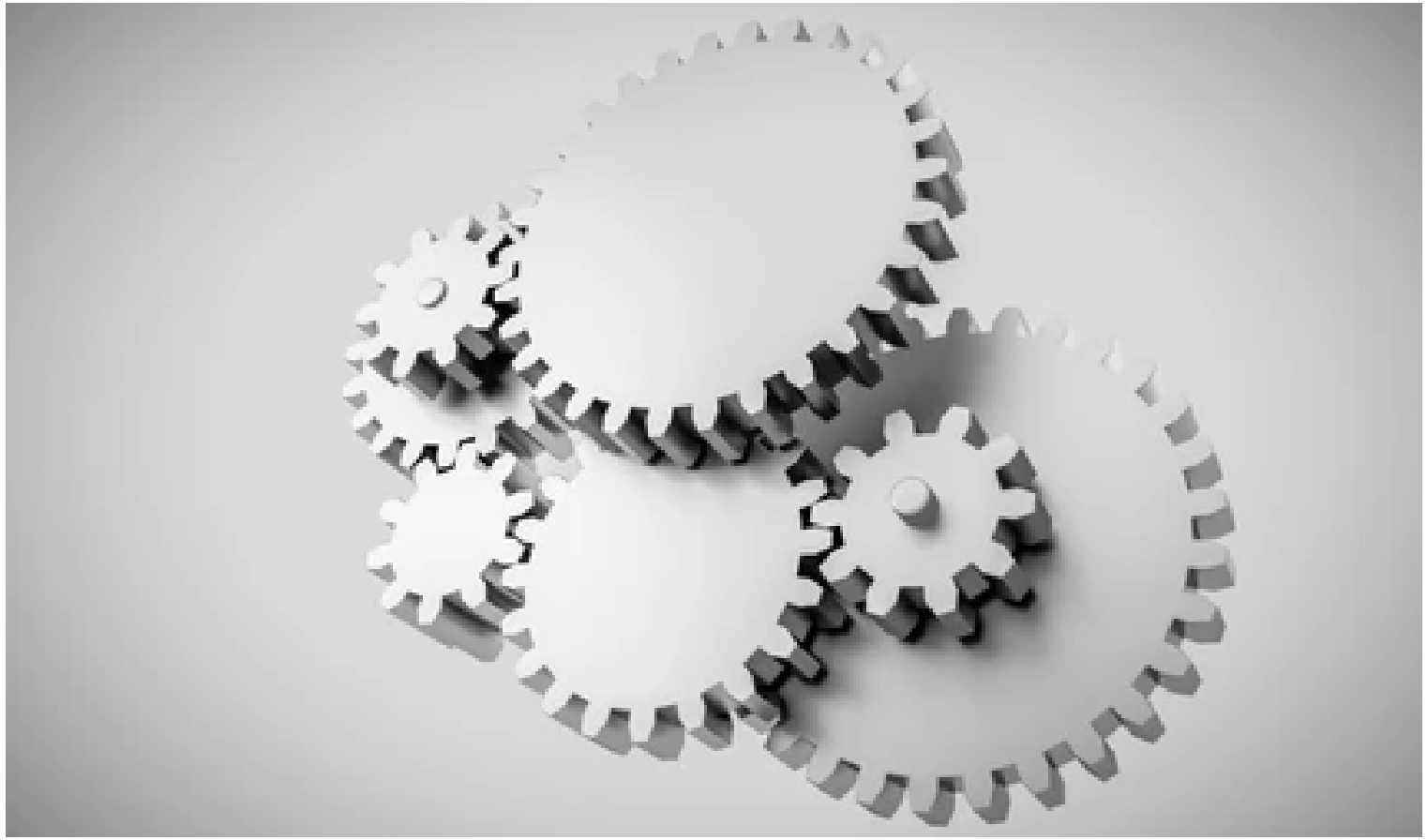
✓Herbal drugs (1433)
✓Essential oils (2098)

344 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)

The *European Pharmacopoeia* (*Ph. Eur.*)

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

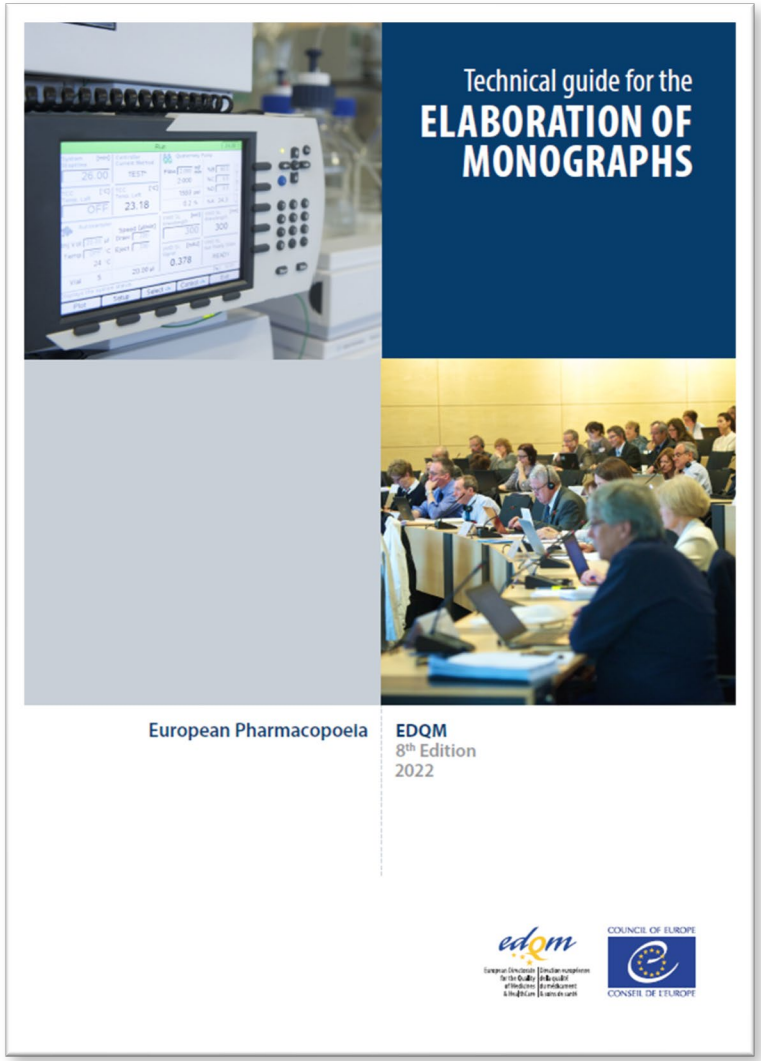


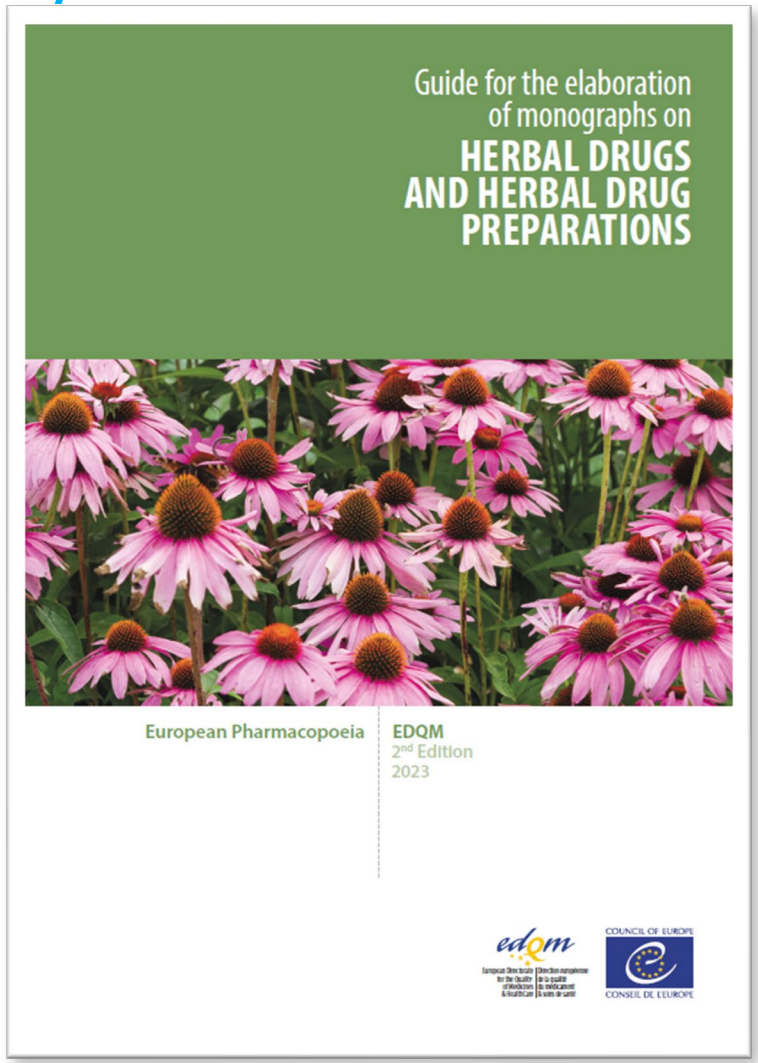
The *European Pharmacopoeia (Ph. Eur.)*

Guides for the elaboration of monographs

2022

[General guide]





2023

[Guide for herbals]

The *European Pharmacopoeia (Ph. Eur.)*

FAQ & HelpDesk – EDQM all activities

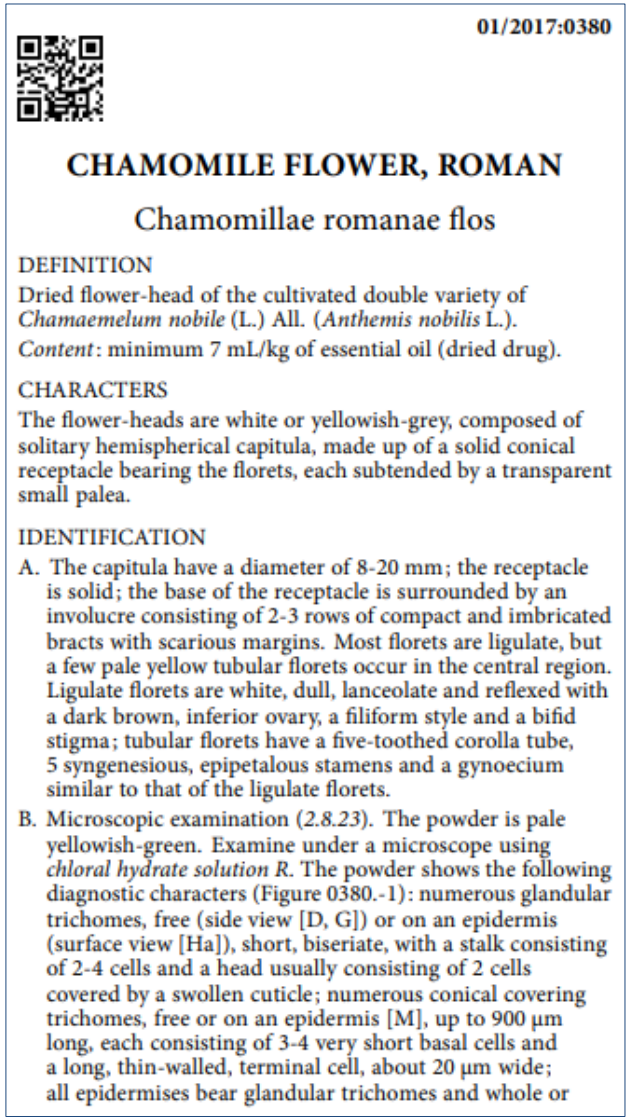
FAQ & HelpDesk

Ph. Eur. monographs on herbal drugs

Main sections

- Title
- Definition
- Identification
- Tests
- Assay

There may be additional sections on characters, storage, labelling



01/2017:0380

CHAMOMILE FLOWER, ROMAN

Chamomillae romanae flos

DEFINITION

Dried flower-head of the cultivated double variety of *Chamaemelum nobile* (L.) All. (*Anthemis nobilis* L.).

Content: minimum 7 mL/kg of essential oil (dried drug).

CHARACTERS

The flower-heads are white or yellowish-grey, composed of solitary hemispherical capitula, made up of a solid conical receptacle bearing the florets, each subtended by a transparent small palea.

IDENTIFICATION

A. The capitula have a diameter of 8-20 mm; the receptacle is solid; the base of the receptacle is surrounded by an involucre consisting of 2-3 rows of compact and imbricated bracts with scarious margins. Most florets are ligulate, but a few pale yellow tubular florets occur in the central region. Ligulate florets are white, dull, lanceolate and reflexed with a dark brown, inferior ovary, a filiform style and a bifid stigma; tubular florets have a five-toothed corolla tube, 5 syngenesious, epipetalous stamens and a gynoecium similar to that of the ligulate florets.

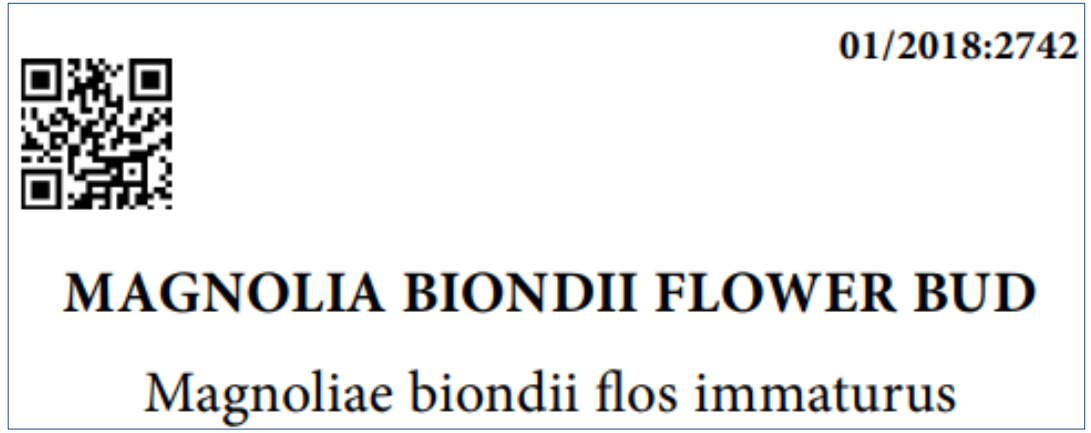
B. Microscopic examination (*2.8.23*). The powder is pale yellowish-green. Examine under a microscope using *chloral hydrate solution R*. The powder shows the following diagnostic characters (Figure 0380.-1): numerous glandular trichomes, free (side view [D, G]) or on an epidermis (surface view [Ha]), short, biseriate, with a stalk consisting of 2-4 cells and a head usually consisting of 2 cells covered by a swollen cuticle; numerous conical covering trichomes, free or on an epidermis [M], up to 900 µm long, each consisting of 3-4 very short basal cells and a long, thin-walled, terminal cell, about 20 µm wide; all epidermises bear glandular trichomes and whole or

Ph. Eur. monographs on herbal drugs

Title

Includes:

- English (or French) name
- Latin name
- For TCM: Chinese name included during the public enquiry but not in the final monograph. Available in chapter *5.22* and in Knowledge database.



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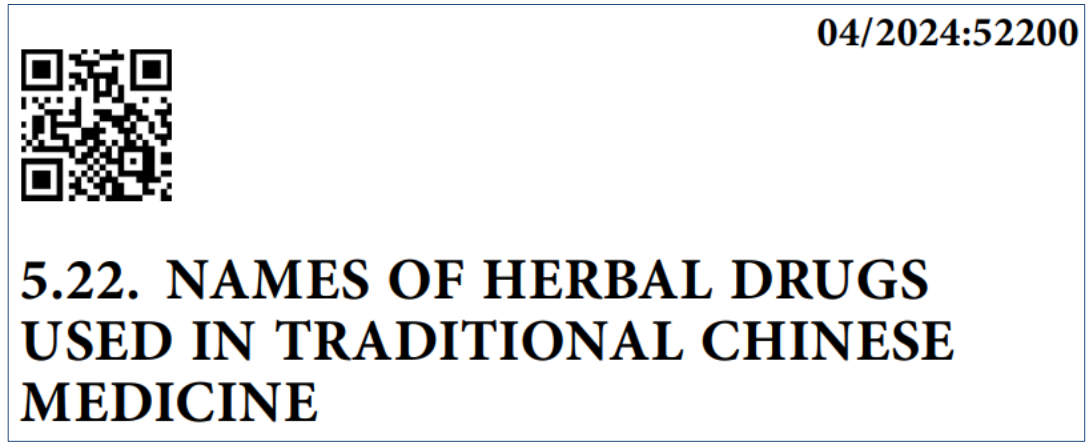
MAGNOLIA BIONDII FLOWER BUD

Magnoliae biondii flos immaturus



04/2024:52200

5.22. NAMES OF HERBAL DRUGS USED IN TRADITIONAL CHINESE MEDICINE

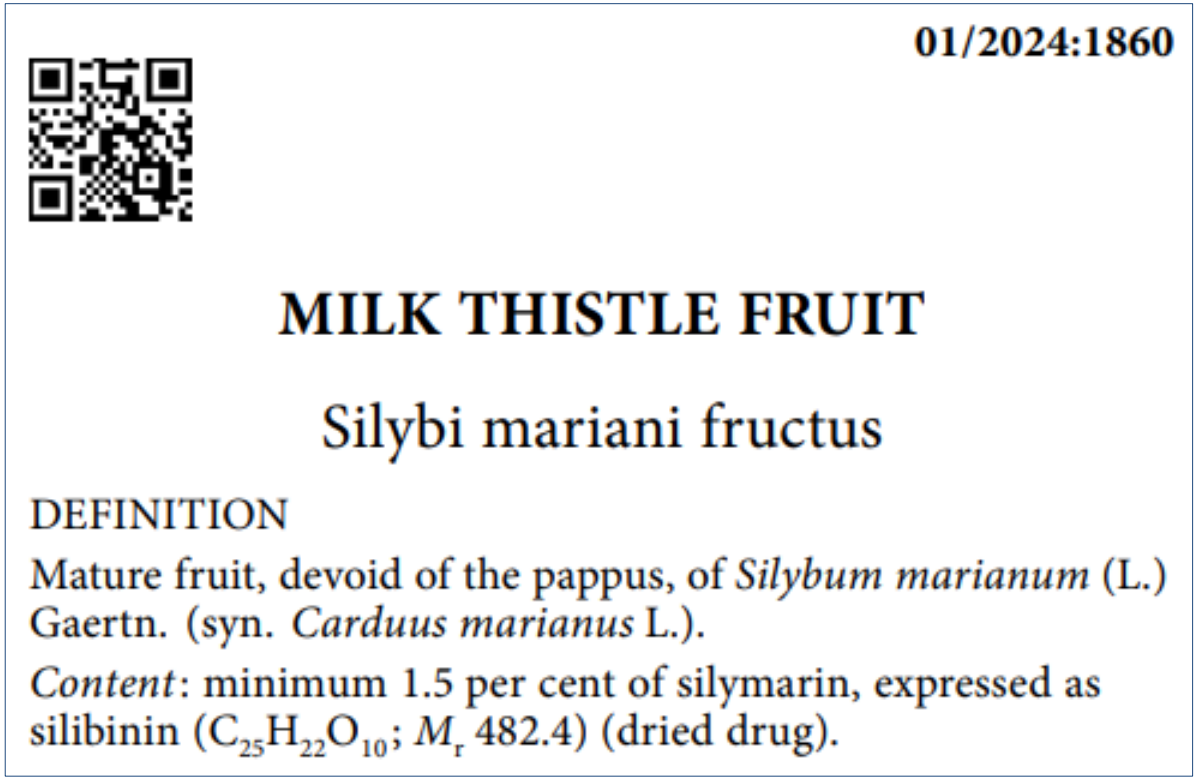
Monograph number	Latin title	English title	Pinyin	Sinogram
2742	Magnoliae biondii flos immaturus	Magnolia biondii flower bud	*xinyi*	辛夷

Ph. Eur. monographs on herbal drugs

Definition

Usually includes :

- the **state of the drug**
- the complete **scientific name** of the plant
- the **part/s** of the plant used
- where appropriate, the **stage in the growth cycle**
- wherever possible, the **minimum content** of quality related constituents



01/2024:1860

MILK THISTLE FRUIT

Silybi mariani fructus

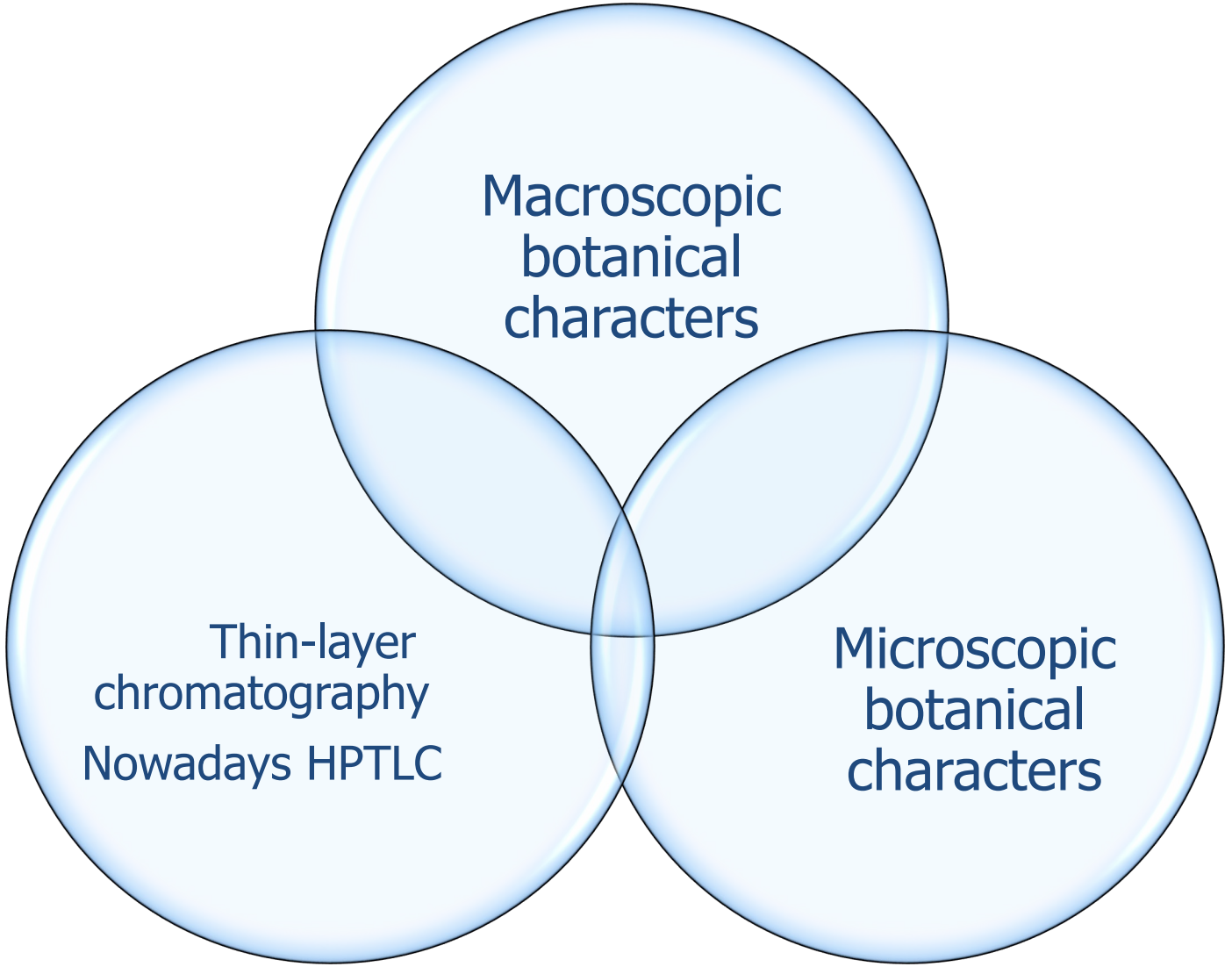
DEFINITION

Mature fruit, devoid of the pappus, of *Silybum marianum* (L.) Gaertn. (syn. *Carduus marianus* L.).

Content: minimum 1.5 per cent of silymarin, expressed as silibinin ($C_{25}H_{22}O_{10}$; M_r 482.4) (dried drug).

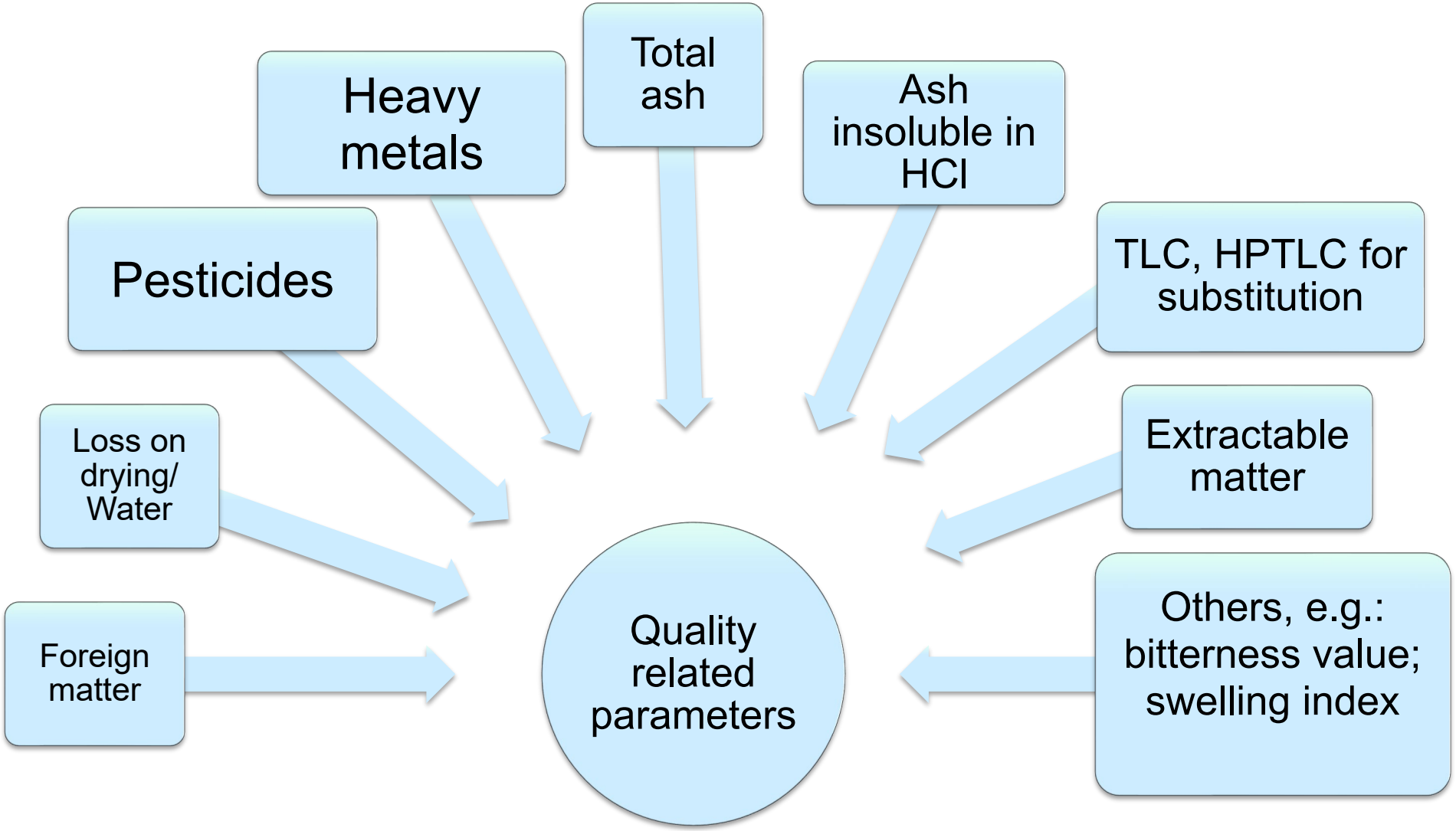
Ph. Eur. monographs on herbal drugs

Identification



Ph. Eur. monographs on herbal drugs

Tests



Ph. Eur. monographs on herbal drugs

Assay

Assays of specific constituents are normally performed to determine the content of:

- *Constituents with known therapeutic activity*
- *Active markers: constituents accepted to substantially contribute to the therapeutic activity*
- *Analytical markers: constituents that serve solely for analytical purposes.*

Often chromatographic assays using reference standards (CRS or HRS)

Non-specific assays for groups of constituents are often performed by spectrophotometric methods (e.g. determination of flavonoids or of total alkaloids)

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Pre-published on the EDQM website on 4 October 2023 !!

Cannabis news

The monograph will be published in Ph. Eur. Supplement 11.5 in January 2024, with an implementation date of 1 July 2024.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Background

Main materials employed in the elaboration of this monograph:

- The monograph of the Dutch Office of Medicinal Cannabis;
- The national monographs in Germany, Denmark and Switzerland;
- Samples of the herbal drug used in The Netherlands as medicinal products;
- Samples of the herbal drug used in Switzerland for extraction.

Ministry of Health, Welfare and Sport

Office of Medicinal Cannabis
P.O. box 16114
2500 BC The Hague
www.cannabisbureau.nl

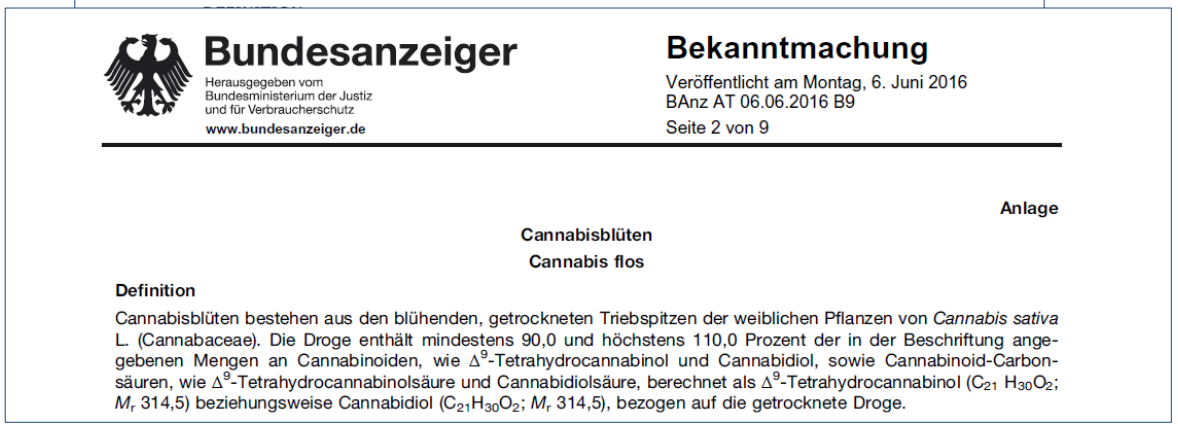
The Office of Medicinal Cannabis is part of the CIBG agency of the Ministry of Health, Welfare and Sport.

Office of Medicinal Cannabis

Monograph Cannabis Flower
Cannabis Flos

Version 8.0
November 01, 2021

General note: The following monograph is elaborated by the Dutch Office of Medicinal Cannabis (OMC). The methods and specifications further described are elaborated conform the EDQM guideline "*Guide for the elaboration of monographs on herbal drugs and herbal drug preparations*" and where applicable refer to general Ph. Eur. chapters.



Bundesanzeiger
Herausgegeben vom Bundesministerium der Justiz und für Verbraucherschutz
www.bundesanzeiger.de

Bekanntmachung
Veröffentlicht am Montag, 6. Juni 2016
BAnz AT 06.06.2016 B9
Seite 2 von 9

Anlage

Cannabisblüten
Cannabis flos

Definition

Cannabisblüten bestehen aus den blühenden, getrockneten Triebspitzen der weiblichen Pflanzen von *Cannabis sativa* L. (Cannabaceae). Die Droge enthält mindestens 90,0 und höchstens 110,0 Prozent der in der Beschriftung angegebenen Mengen an Cannabinoiden, wie Δ^9-Tetrahydrocannabinol und Cannabidiol, sowie Cannabinoid-Carbonsäuren, wie Δ^9-Tetrahydrocannabinolsäure und Cannabidiolsäure, berechnet als Δ^9-Tetrahydrocannabinol (C_{21} $H_{30}O_2$; M_r 314,5) beziehungsweise Cannabidiol ($C_{21}H_{30}O_2$; M_r 314,5), bezogen auf die getrocknete Droge.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Scope

The new *Ph. Eur.* monograph on *Cannabis flos (3028)* covers the herbal drug:

- Employed as raw material for the production of **extracts**,
- Or prescribed as is, to be taken by patients by inhalation or oral administration (i.e. prescribed to patients as a **medicinal product**).

Additional requirements have been included in the limits for content, in the production section and in the tests for foreign matter, arsenic, cadmium and lead for cases in which the herbal drug is to be **prescribed to patients**.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Title

CANNABIS FLOWER

Cannabis flos

DEFINITION

Dried, whole or fragmented, fully developed female inflorescence of *Cannabis sativa* L.

The title includes an established term for this herbal drug, i.e. "the flower".

DEFINITION sections in monographs are where herbal drugs are described accurately, i.e. "fully developed female inflorescence"

Thousands of fully developed female flowers of about 2 mm long (left) are found in fully developed female inflorescences (right)

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Definition

DEFINITION

Dried, whole or fragmented, fully developed female inflorescence of *Cannabis sativa* L.

Content: if the herbal drug is to be prescribed to patients as a medicinal product, the measured contents of total tetrahydrocannabinol and total cannabidiol, respectively, do not deviate from the values stated on the label by more than ± 10 per cent.

THC-dominant type:

- *total tetrahydrocannabinol, expressed as Δ⁹-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): minimum 5.0 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-intermediate type:

- *total tetrahydrocannabinol, expressed as Δ⁹-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): minimum 1.0 per cent (dried drug);
- *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): minimum 1.0 per cent (dried drug);
- *total tetrahydrocannabinol / total cannabidiol ratio*: 0.2 to 5.0 (dried drug).

CBD-dominant type:

- *total tetrahydrocannabinol, expressed as Δ⁹-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): minimum 5.0 per cent (dried drug).

All the limits for content concern:

- Total tetrahydrocannabinol, i.e. the sum of Δ^9-tetrahydrocannabinol (**Δ^9-THC**), and Δ^9-tetrahydrocannabinolic acid (**Δ^9-THCA**) expressed as Δ^9-tetrahydrocannabinol.
- Total cannabidiol, i.e. the sum of cannabidiol (**CBD**), and cannabidiolic acid (**CBDA**) expressed as cannabidiol.

Data available would not support prescribing analytical procedures and specifications for content **for other cannabinoids** or **terpenes** → *we are not aware of the existence of approved specifications for minor cannabinoids or for terpenes, in cannabis in Europe*

However, the LC-UV procedure described in the monograph is selective for a total of **17 cannabinoids** that can be detected well below 1 per cent:

- Δ^9-THC, Δ^9-THCA, CBD and CBDA, as well as **CBC**, **CBCA**, **CBDV**, **CBDVA**, **CBG**, **CBGA**, **CBL**, **CBLA**, **CBN**, **CBNA**, **THCV**, **THCVA** and **Δ^8-THC**.

This is not mentioned in the official text but can be observed in the chromatograms available in the knowledge database

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Definition

DEFINITION

Dried, whole or fragmented, fully developed female inflorescence of *Cannabis sativa* L.

Content: if the herbal drug is to be prescribed to patients as a medicinal product, the measured contents of total tetrahydrocannabinol and total cannabidiol, respectively, do not deviate from the values stated on the label by more than ± 10 per cent.

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

THC/CBD-intermediate type:

- *total tetrahydrocannabinol, expressed as Δ⁹-tetrahydrocannabinol* ($C_{21}H_{30}O_2$; M_r 314.5): minimum 1.0 per cent (dried drug);
- *total cannabidiol, expressed as cannabidiol* ($C_{21}H_{30}O_2$; M_r 314.5): minimum 1.0 per cent (dried drug);
- *total tetrahydrocannabinol / total cannabidiol ratio*: 0.2 to 5.0 (dried drug).

CBD-dominant type:

- *total tetrahydrocannabinol, expressed as Δ⁹-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): minimum 5.0 per cent (dried drug).

- This tight requirement is considered necessary from a **patient safety** perspective **if** the herbal drug is to be prescribed to patients as a medicinal product → *thus ensuring a high degree of certainty about the potency of THC and CBD prescribed and dispensed to patients. This is specially relevant due to the high bioactivity of both THC and CBD.*

This tight requirement is **not** considered necessary if the herbal drug is used for **extraction**, since there are different variables in determining the potency of a preparation independent of the raw material.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Production

Ph. Eur. General Notices: […] Statements in the Production section draw attention to particular aspects of the manufacturing process but are not necessarily exhaustive. They constitute mandatory requirements for manufacturers […]

> PRODUCTION
>
> If the herbal drug is to be prescribed to patients as a medicinal product, the inflorescence is cut at the base with minimal rachis remaining.

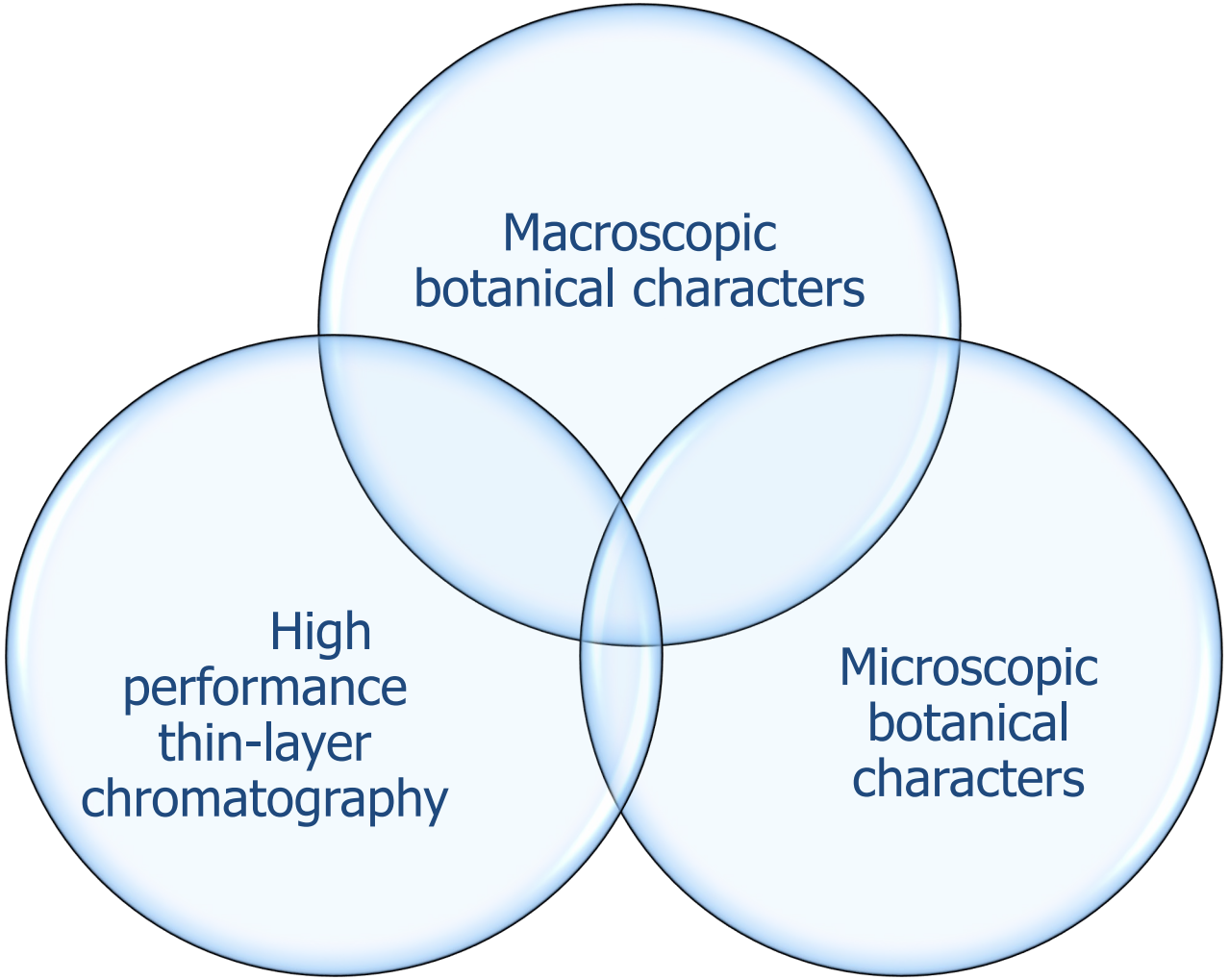
A statement on limiting the presence of rachis/stalk in the herbal drug is included only in the **PRODUCTION** section, since it involves a particular aspect of the **manufacturing process**, *i.e. cutting the inflorescence from the rest of the plant when harvesting and/or in further steps of the manufacturing process.*

Unfeasible to prescribe a **limit** on the presence of rachis/stalk in the herbal drug, which in other monographs is often based on maximum diameter and introduced in the test for Foreign matter → *because the cannabis inflorescence itself contains rachis/stalk.*

This requirement is considered necessary only if the herbal drug is to be prescribed to patients as a **medicinal product**, partly as an excess of rachis/stalk may make the inhalation of the heated herbal drug unpleasant.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Identification



The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Macroscopic botanical characters

Guide for the elaboration of monographs on herbal drugs and herbal drug preparations: *[…] The main macroscopic botanical characters of the herbal drug are specified to permit a clear identification […].*

IDENTIFICATION

A. Depending on the variety, the colour of the herbal drug varies from dark green to pale yellow or from light brown to reddish-brown. The whole female inflorescence is a dense or more or less lax panicle, comprising sessile or almost sessile, elongated bracts (about 10 mm long) with dentate margins, intermingled with the flowers. The fragmented inflorescence, comprises parts of the axis of the inflorescence, the bracts and panicle, together with individual flowers or floral organs. The female flowers are very small (about 2 mm) with a short pedicel. The perianth is monosepalous and apetalous. The sepal, often referred to as the bracteole, is wrapped around the unilocular ovary which bears two styles, each terminating in a fine,

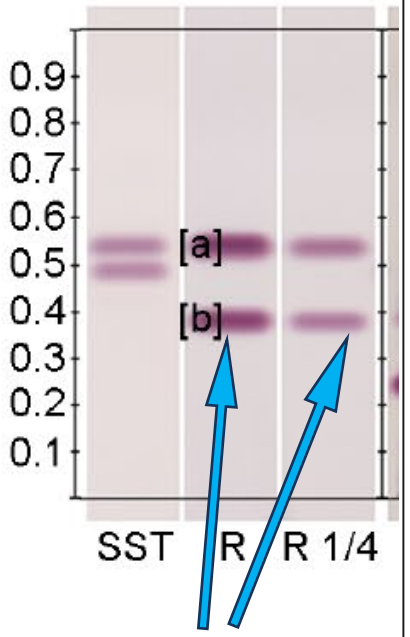
Leaves can be present intermingled with the flowers.

But leaves are not mentioned in this identification test because when young, these may not be able to be differentiated from bracts, which are part of the inflorescence and rich in trichomes.

A limit regarding the leaves is included in the test for Foreign matter.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

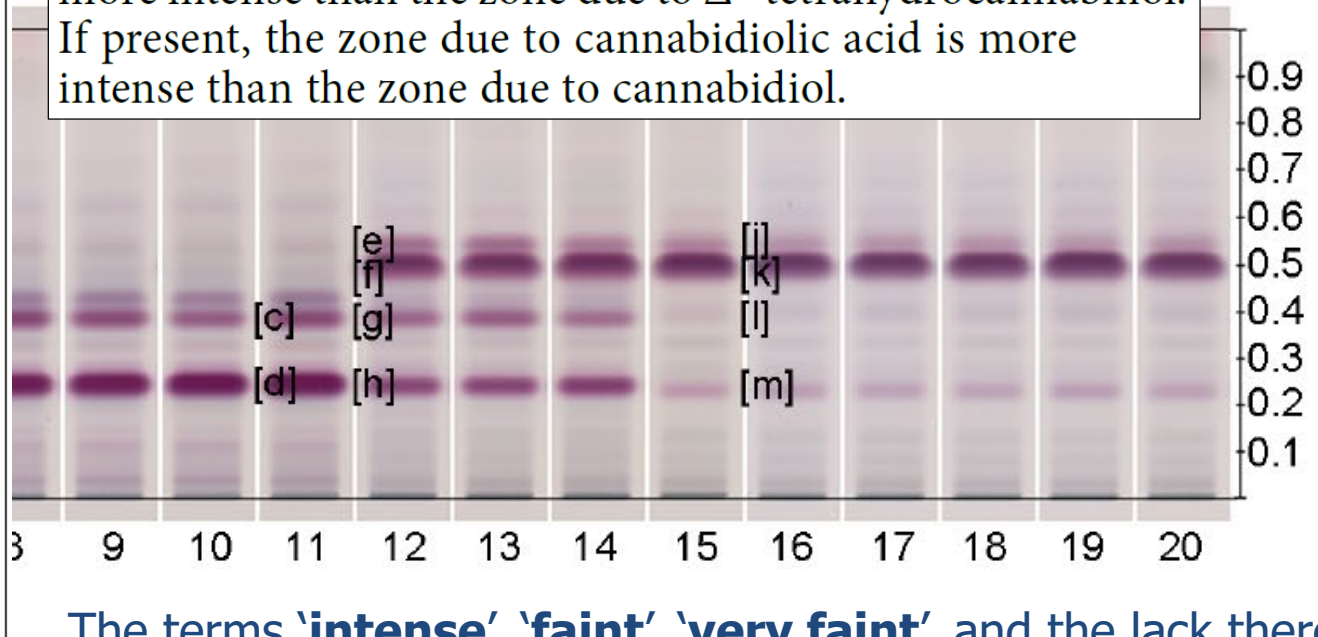
Identification by HPTLC



Intensity marker: Δ⁹-THC

Top of the plate			
Cannabidiol: a reddish-violet zone		A reddish-violet zone, faint to very faint (cannabidiol) A reddish-violet zone, intense (cannabidiolic acid)	A reddish-violet zone, faint to very faint (cannabidiol) A reddish-violet zone, intense (cannabidiolic acid)
Δ⁹-Tetrahydrocannabinol: a reddishviolet zone	A reddish-violet zone, faint to equivalent (Δ⁹-tetrahydrocannabinol)	A reddish-violet zone, faint (Δ⁹-tetrahydrocannabinol)	A grey to reddish-violet zone, very faint, may be absent (Δ⁹-tetrahydrocannabinol)
	A reddish-violet zone, intense (Δ⁹-tetrahydrocannabinolic acid)	A reddish-violet zone (Δ⁹-tetrahydrocannabinolic acid)	A reddish-violet zone, very faint (Δ⁹-tetrahydrocannabinolic acid)
Reference solution (a)	**Test solution (THC-dominant type)**	**Test solution (THC/CBD-intermediate type)**	**Test solution (CBD-dominant type)**

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



The terms '**intense**', '**faint**', '**very faint**', and the lack thereof, need to be interpreted according to chapter *High-performance thin-layer chromatography (2.8.25)*

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Tests

Tests described in the monograph

- Total CBN (by LC-UV)
- Foreign matter
- Loss on drying
- Arsenic
- Cadmium
- Lead
- Mercury

Tests applicable according to general monograph *Herbal drugs (1433)*

- Pesticides
- Aflatoxin B_1
- Microbial contamination, if the herbal drug is to be prescribed to patients as a medicinal product

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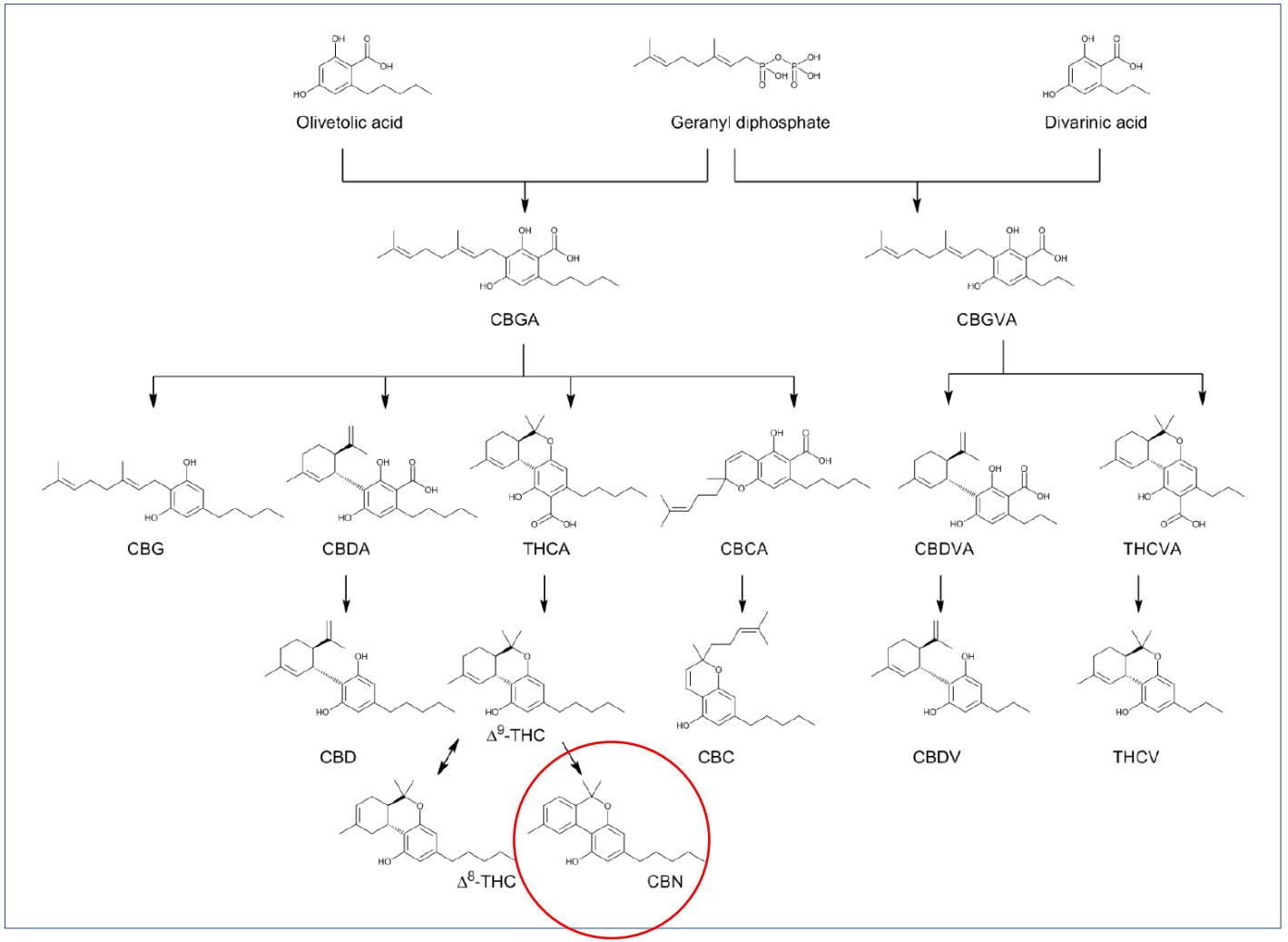
Test for Total CBN by LC-UV



Total CBN = sum of cannabinol (**CBN**), and cannabinolic acid (**CBNA**) expressed as CBN = maximum 1.0 per cent

There are two main degradation processes:

- Thermal: acids are decarboxylated to their corresponding neutral forms (e.g. Δ^9-THCA to Δ^9-THC, CBDA to CBD, or **CBNA** to **CBN**).
- Oxidation (e.g. Δ^9-THC to **CBN**).

Contents of more than 1.0 per cent of CBN imply a significant degradation of the herbal drug.

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Test for Total CBN by LC-UV

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**

↑Quantitations 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

Total CBN. Liquid chromatography (*2.2.29*).

Test solution (a). To 0.50 g of the cut or milled 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. 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 0.22 µm).

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 10.0 mL of reference solution (a) to 25.0 mL with *methanol R*.

Reference solution (d). To 50 mg of *cannabis flower for system suitability HRS* in a suitable centrifuge tube fitted with a screw cap, add 4 mL of *ethanol (96 per cent) R* and shake for 15 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 0.22 µm).

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

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Test for Total CBN by LC-UV

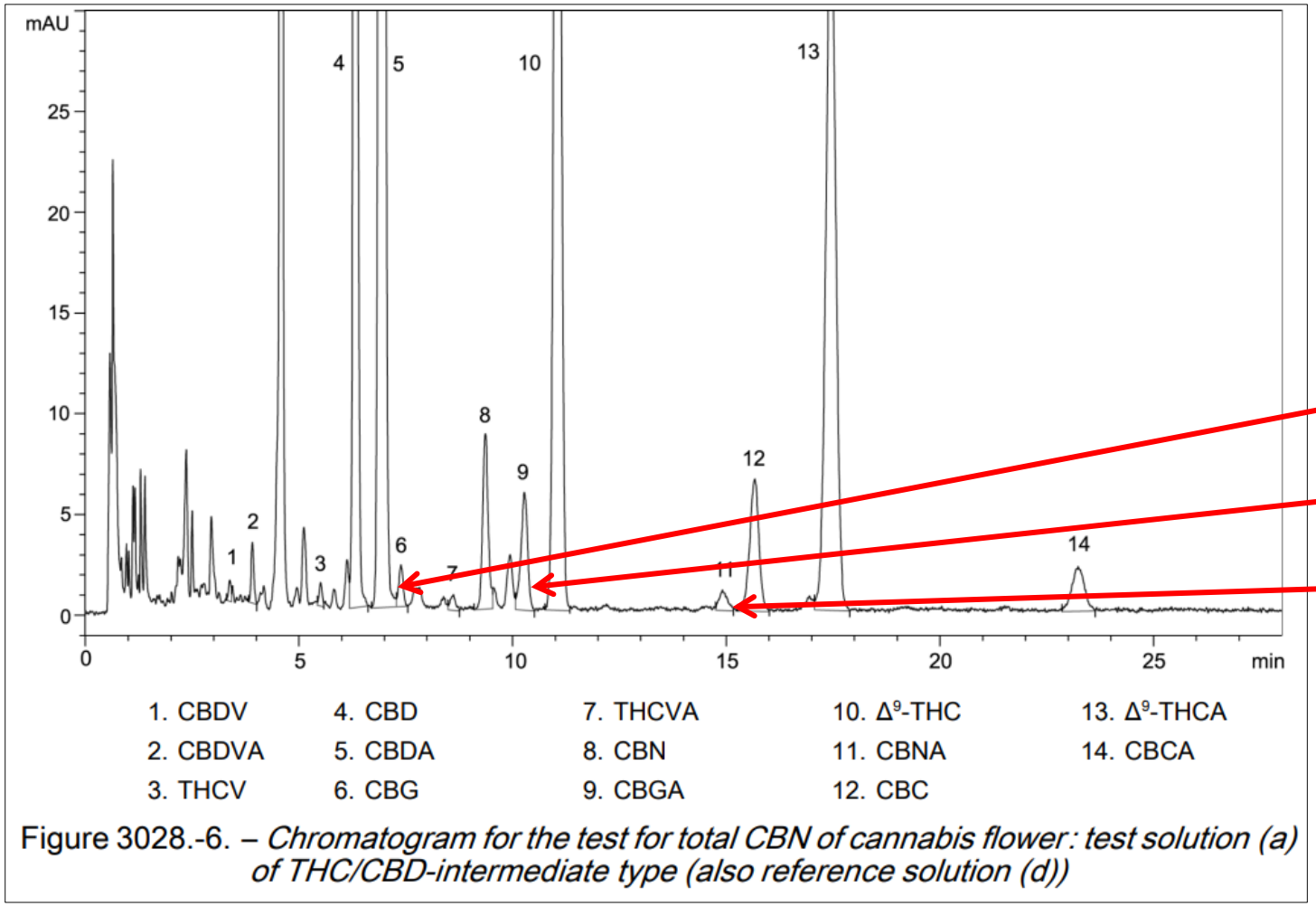

Figure 3028.-6. – *Chromatogram for the test for total CBN of cannabis flower: test solution (a) of THC/CBD-intermediate type (also reference solution (d))*

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 1.5, 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.

min 1.5 p/v ratio between CBG & CBDA

min 2.0 *Rs* between CBGA & Δ^9-THC

min 5.0 p/v ratio between CBNA & CBC

System suitability test containing three acceptance criteria

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Test for Foreign matter

The specific requirements regarding **seeds** and **leaves** are considered necessary only if the herbal drug is to be prescribed to patients as a **medicinal product**, partly as seeds and excess of leaves may make the inhalation of the heated herbal drug unpleasant

Foreign matter (*2.8.2*): maximum 2 per cent; if the herbal drug is to be prescribed to patients as a medicinal product, 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.

With regards to the presence of powdery mildew or other moulds, *no ad-hoc* specification is included in the monograph but this is covered by chapter on ***Foreign matter (2.8.2)*** → *implying that producers need to perform in-house risk evaluations for controlling mould, where the sampling procedure and the expected appearance of the material is defined by producers. The control of mould must be covered by GACP (Good Agricultural and Collection Practice)*

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.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Test for Loss on drying

Loss on drying (*2.2.32*): maximum 12.0 per cent, determined on 1.000 g of the cut or milled herbal drug (not sieved) by drying over about 100 g of *molecular sieve R* at a pressure between 1.5 kPa and 2.5 kPa at 40 °C for 24 h.

Necessary to perform this test at low temperature (40°C) and under 'medium vacuum', in order to minimise the evaporation of volatile content other than due to water (e.g. essential oil / terpenes).

Other proposals received during Pharmeuropa enquiry to control for moisture in the herbal drug:

- **Determination of water by Karl-Fischer analysis**

  Advantage: it would provide a quantitative determination of water in the herbal drug;

  Disadvantage: lack of sufficient data to prescribe a limit for water.

- **Determination of water activity**

  Disadvantage: consists of a 'simple' determination of relative humidity requiring an hygrometer and temperature-measuring device not often used in routine QC. Also lack of sufficient data to prescribe a limit for water activity.

The determination of water by Karl-Fischer analysis may be considered in the future

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Test for Elemental impurities

Arsenic (*2.4.27*): maximum 0.2 ppm if the herbal drug is to be prescribed to patients as a medicinal product.

Cadmium (*2.4.27*): maximum 1.0 ppm, or maximum 0.3 ppm if the herbal drug is to be prescribed to patients as a medicinal product.

Lead (*2.4.27*): maximum 5.0 ppm, or maximum 0.5 ppm if the herbal drug is to be prescribed to patients as a medicinal product.

Mercury (*2.4.27*): maximum 0.1 ppm.

If the herbal drug is not used as a medicinal product, the same limits as in the general monograph ***Herbal drugs (1433)*** apply.

Otherwise, the limits in **ICH Q3D** for Class I elements based on inhalation permitted daily exposure apply

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Test for Pesticides

According to general monograph ***Herbal drugs (1433):***

> **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.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Test for Aflatoxins

According to general monograph ***Herbal drugs (1433):***

> **Aflatoxin B_1** (*2.8.18*). Where necessary, limits for aflatoxins may be required.

And according to general chapter ***Determination of aflatoxin B_1 in herbal drugs (20818):***

> Unless otherwise indicated in the monograph, herbal drugs contain not more than 2 µg/kg of aflatoxin B_1. The competent authority may also require compliance with a limit of 4 µg/kg for the sum of aflatoxins B_1, B_2, G_1 and G_2.

Therefore, it is not allowed to market a herbal drug batch containing more than 2 µg/Kg of aflatoxin B_1

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Test for Microbial contamination

According to general monograph ***Herbal drugs (1433):***

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)).

Therefore, if the herbal drug is used as a **medicinal product**, the limits in chapters *5.1.8* and *5.1.4* apply

Different limits are given in chapters *5.1.8* and *5.1.4* depending on:

- Whether the herbal drug is intended for the preparation of infusions and decoctions using boiling water;
- Whether the method of processing or pre-treatment reduces the levels of organisms to certain levels;
- The route of administration.

Even though this is the first monograph of a herbal drug that is used as such for inhalation, hence presenting an additional layer of complexity, no limits for microbial contamination were introduced in the monograph as users are assumed to be familiar enough interpreting chapters 5.1.8 and 5.1.4.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Others

No tests for **Ochratoxin A** or **other aflatoxins than Aflatoxin B1**, are included in the monograph because *Cannabis flos* does not present a particular high risk from being affected from fungi infection resulting in the production of these toxins. For example, *Cannabis flos* does not present a particular high content of sugars.

No test for **Total ash** is included in the monograph because mineral contamination is expected to be very low in *Cannabis flos*.

But the addition of a test for Total ash in the monograph may be considered in the future as this type of test is often present in monographs of herbal drugs regardless of the likelihood of mineral contamination, and as cannabis flower is known to contain crystals of calcium oxalate.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Assay by LC-UV

The range for which the assay procedure has been validated for is indicated

ASSAY

This procedure has been validated for an analytical range of 0.2 per cent to 32.0 per cent of Δ⁹-tetrahydrocannabinol, Δ⁹-tetrahydrocannabinolic acid, cannabidiol and cannabidiolic acid respectively.

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.

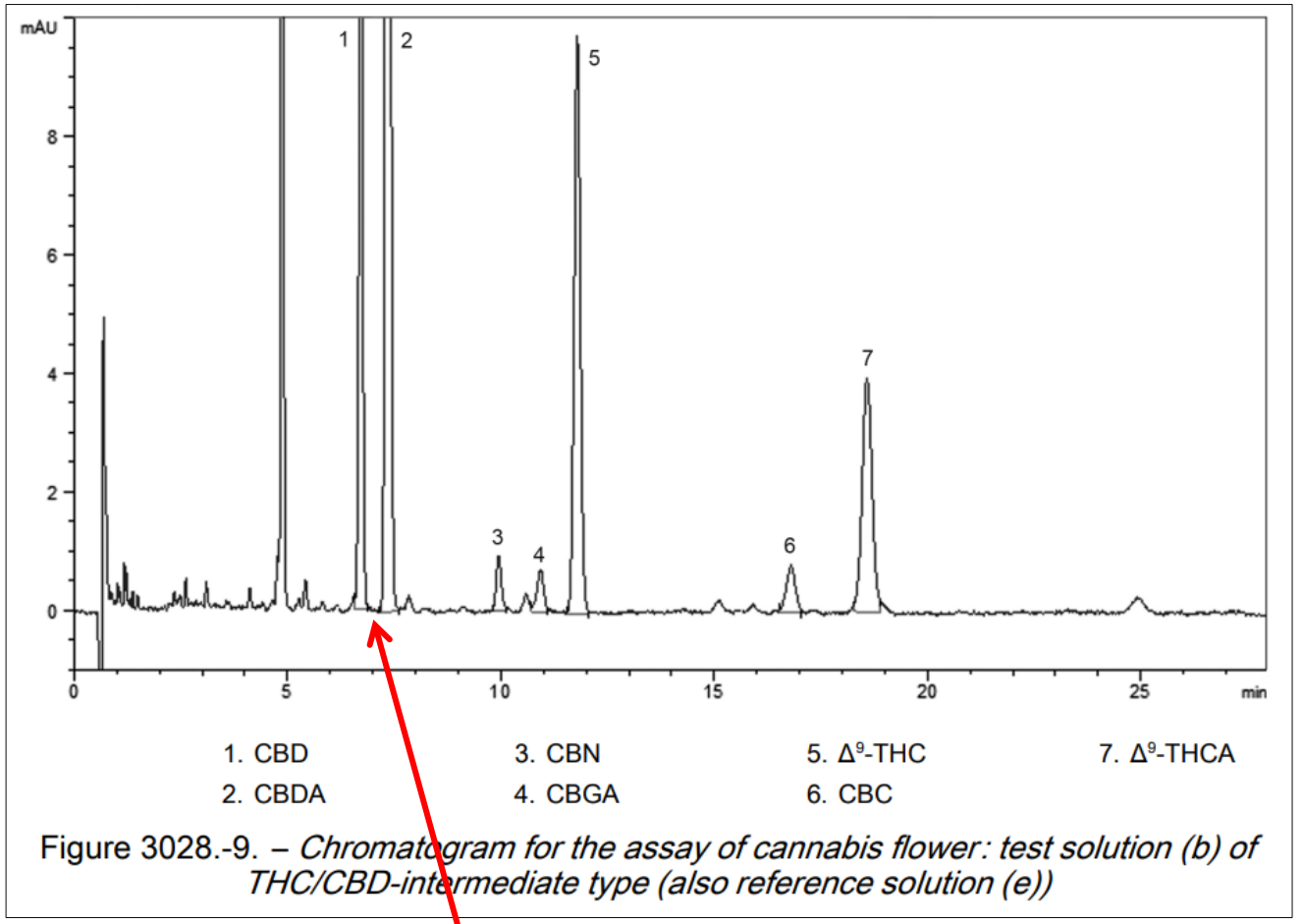

Figure 3028.-9. – *Chromatogram for the assay of cannabis flower: test solution (b) of THC/CBD-intermediate type (also reference solution (e))*

SST: min 2.0 Rs between CBD & CBDA

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Assay by LC-UV, calculation formulas

Total THC

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

$$\frac{((A_1 \times 1.097) + (A_3 \times 0.691 \times 0.877)) \times m_2 \times p \times 4}{A_2 \times m_1}$$

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*;

1.097 = correction factor of Δ^9-tetrahydrocannabinol with reference to cannabidiol;

0.691 = 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.

Total CBD

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

$$\frac{(A_1 + (A_3 \times 0.596 \times 0.877)) \times m_2 \times p \times 4}{A_2 \times m_1}$$

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*;

0.596 = correction factor of cannabidiolic acid with reference to cannabidiol;

0.877 = ratio of the molecular mass of cannabidiol to that of cannabidiolic acid.

The new *Ph. Eur.* monograph on *Cannabis flower (3028)*

Storage and labelling

STORAGE

In an airtight container.

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 as a medicinal product.

The first sentence of the LABELLING section is necessary to assess the requirement for content regarding the maximum ± 10 per cent allowed deviation:

Content: if the herbal drug is to be prescribed to patients as a medicinal product, the measured contents of total tetrahydrocannabinol and total cannabidiol, respectively, do not deviate from the values stated on the label by more than ± 10 per cent.

The second sentence of the LABELLING section is necessary to assess the additional requirements in the monograph for content, in the production section and in the tests for foreign matter, arsenic, cadmium and lead **for cases in which the herbal drug is to be prescribed to patients**.

Final remarks

Ph. Eur. texts are updated regularly taking into account changes in marketed products and scientific progress

The *Ph. Eur. Commission* encourages users to propose revisions to a general chapter or monograph already published in the *Ph. Eur.*

- **For manufacturers and other interested parties from Member States of the *Ph. Eur.* Convention**: via the national pharmacopoeia authority.
- **For others** (*manufacturers and other interested parties from non-Member States of the Ph. Eur. Convention or multinational interested parties, for international organisations and for industry associations or other associations*): via the Secretariat in Strasbourg (via the EDQM HelpDesk)

Final remarks

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PHARMEUROPA ONLINE

➢Being part of a dynamic scientific community !!!

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