IDMP ISO-11238 Substance Standard

Structural Diverse Substances

Herbal Medicinal Substance/ Preparations/ Products EU-Regulatory aspects

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MEDICINES
EVALUATION
BOARD

Outline of the presentation

- Regulatory basis and definitions in accordance with the EU Directive and Guidelines;
- Classification of Herbal Extracts according to the European Pharmacopoeia;
- Qualitative and Quantitative Particulars of the Active Substance (s) of a Herbal medicinal product
- Description of the Herbal Substance and Herbal preparation in view of the IDMP ISO- 11238 Standard (Structurally Diverse Substances, source material Herbal Substance;
- Important data elements for unique identification of the Herbal Substance and Herbal Preparation;
- Examples, especially regarding the type of extraction/ manufacturing of the Herbal Preparation.

Definition of Herbal medicinal products:
1) Directive 2004/24/EC:

Herbal medicinal products:

Any medicinal product, *exclusively* containing *as active substances* one or more *herbal substances* or one or more *herbal preparations*, or one or more such herbal substances in combination with one or more such herbal preparations

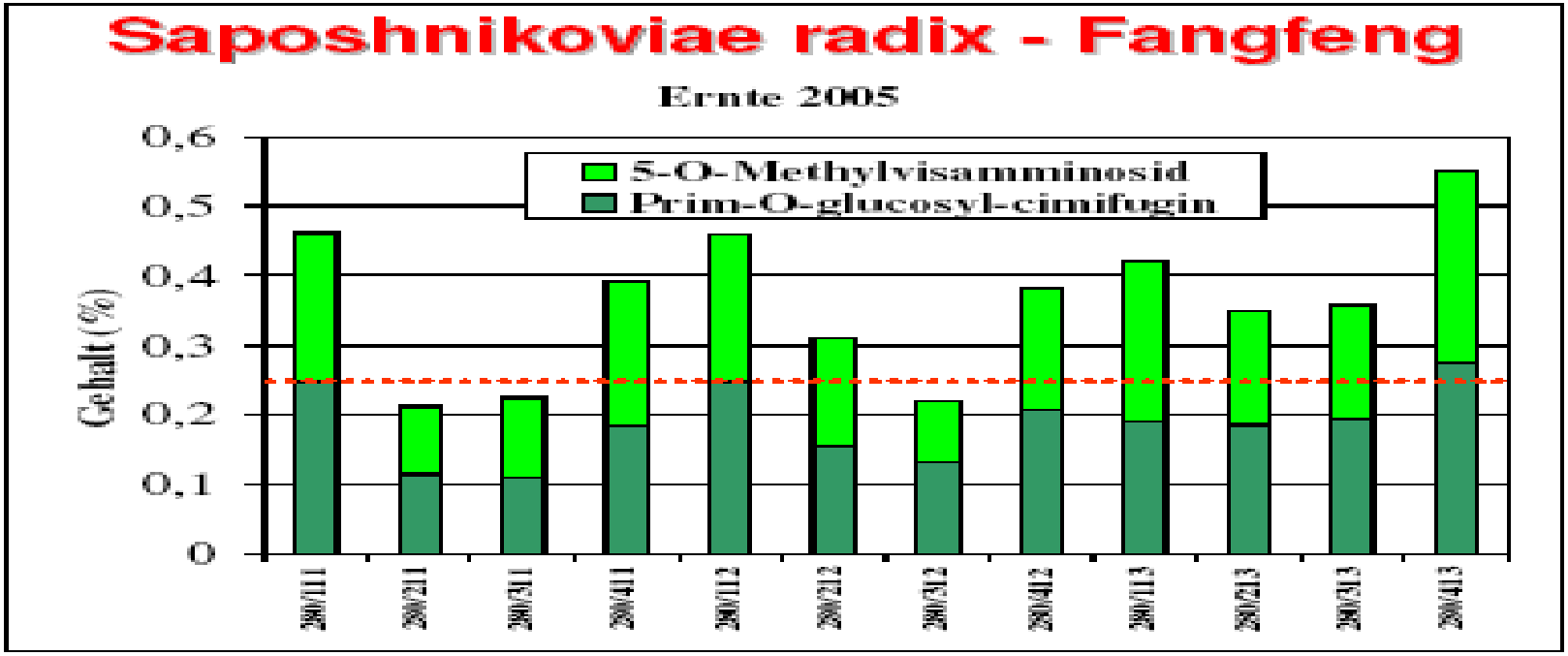
2) Guideline on quality of Herbal Medicinal Products/ Traditional Herbal Medicinal Products:

All herbal substances/ herbal preparations are essentially defined by their production process and their specifications

31 March 2011:
(CPMP/QWP/2819/00 Rev 2, EMEA/CVMP/814/00 Rev 2)

2003/63/EC Preambule (8)

"Herbal medicinal products differ substantially from conventional medicinal products in so far as they are **intrinsically associated with** the very particular notion of **herbal substances and herbal preparations**. It is therefore appropriate to determine **specific requirements** in respect of these products with regard to the standardized marketing authorisation requirements."



Herbal substance → Herbal Preparation → Herbal Medicinal Product

Herbal substance:

- Cultivation/ harvesting / drying conditions
- Microbial levels, aflatoxins, heavy metals, etc.
- Pre-post-harvest chemical treatments (pesticides fumigants)

Herbal Preparation:

- Methods of preparations:
- Drying conditions (microbial levels)
- Microbial purity on storage

Herbal Medicinal Product:

- Manufacturing process (temperature effects, residual solvents)
- Profile and stability of the active constituents
- formulation in packaging

Quality assurance of herbal medicinal products

Quality assurance

- Ensure that that the right plant (part) is used
- Absence of impurities
- Appropriate levels of active constituents and batch to batch consistency

Quality control

- Clear botanical definition
- Test for identity
- Test for purity
  - Adulteration
  - Foreign materials
    - Fumigants
    - Mycotoxins
    - Pesticides
    - Toxic metals
  - Microbial contamination
  - Residual solvents
- Assay for constituents with known therapeutic activity or (active) markers

European Pharmacopoeia Classification of Herbal Extracts

- "*Standardized extracts*": Constituents responsible for the therapeutic activity are known.
- "*Quantified extracts*" No constituents with known therapeutic activity but active markers.
- "*Other extracts*" Active constituents not known.

Qualitative and Quantitative Particulars of the Active Substance (s) of a Herbal Medicinal Product

- **Standardized herbal substances/ herbal preparations** are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardization is achieved by adjustment of the herbal substances/herbal preparations with **excipients or by blending** batches of herbal substances and/or herbal preparations;

- **Example:**

  Sennae folium:

  415 -500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, caculated as sennoside B

Qualitative and Quantitative Particulars of the Active Substance (s) of a Herbal Medicinal Product

- **Quantified herbal substances/ herbal preparations** are adjusted to a defined range of constituents (active markers); **adjustment is exclusively achieved by blending batches** of herbal substances and/or herbal preparations
- **Example:**

  Salicis cortex 4 g, corresponding to 40 to 48 mg of total phenolic glycosides, expressed as salicin.

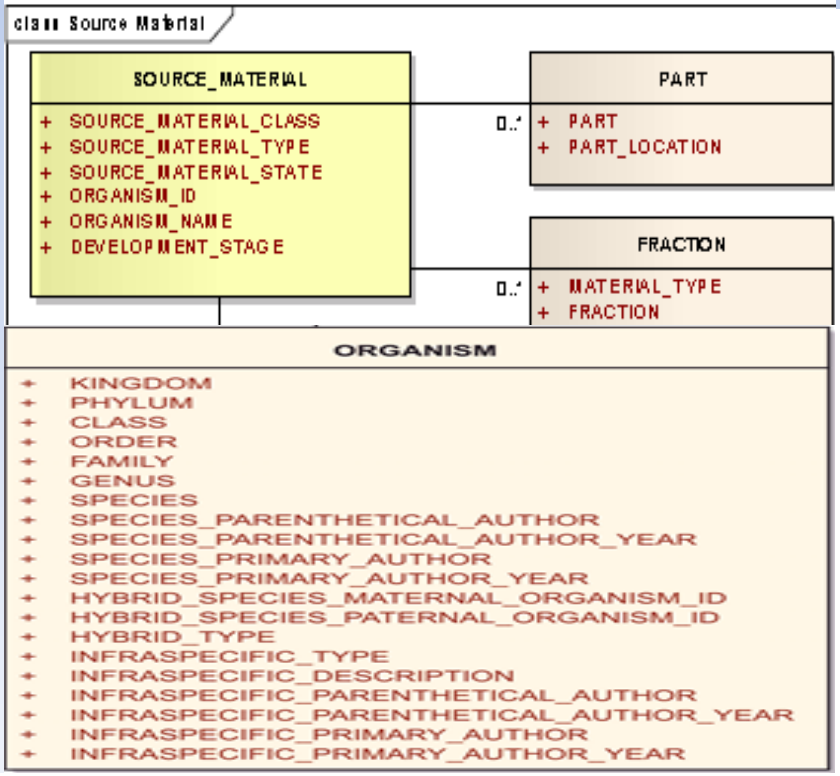
Qualitative and Quantitative Particulars of the Active Substance (s) of a Herbal Medicinal Product

- **Other** herbal substances/herbal preparations are active substances for which neither constituents with known therapeutic activity nor active markers are known. These herbal substances/herbal preparations are **not adjusted** to a defined content of analytical marker.
- **Example:**
  Valerianae Radix 900 mg

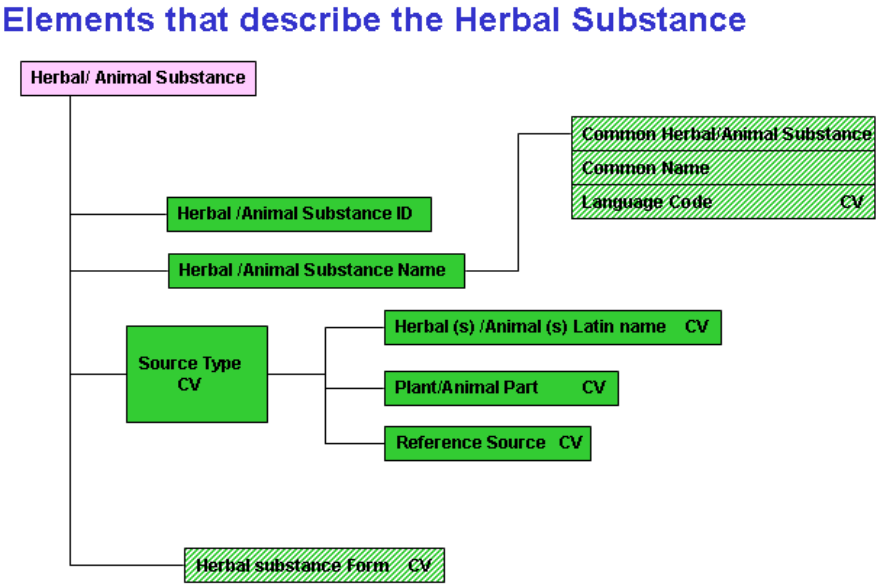
Description according to the IDMP ISO-11238 Standard for Structurally Diverse Substances: “Source Material/Herbal Substance”

- Structurally diverse substances shall be defined by the source material the substance is derived from;
- The parent organism from which the source material was derived shall be essential to the definition of the substance.
  Varieties, cultivars, strains of biological material shall be defining information .
- Herbals are typically described by parent organism (genus, species and part of the plant)

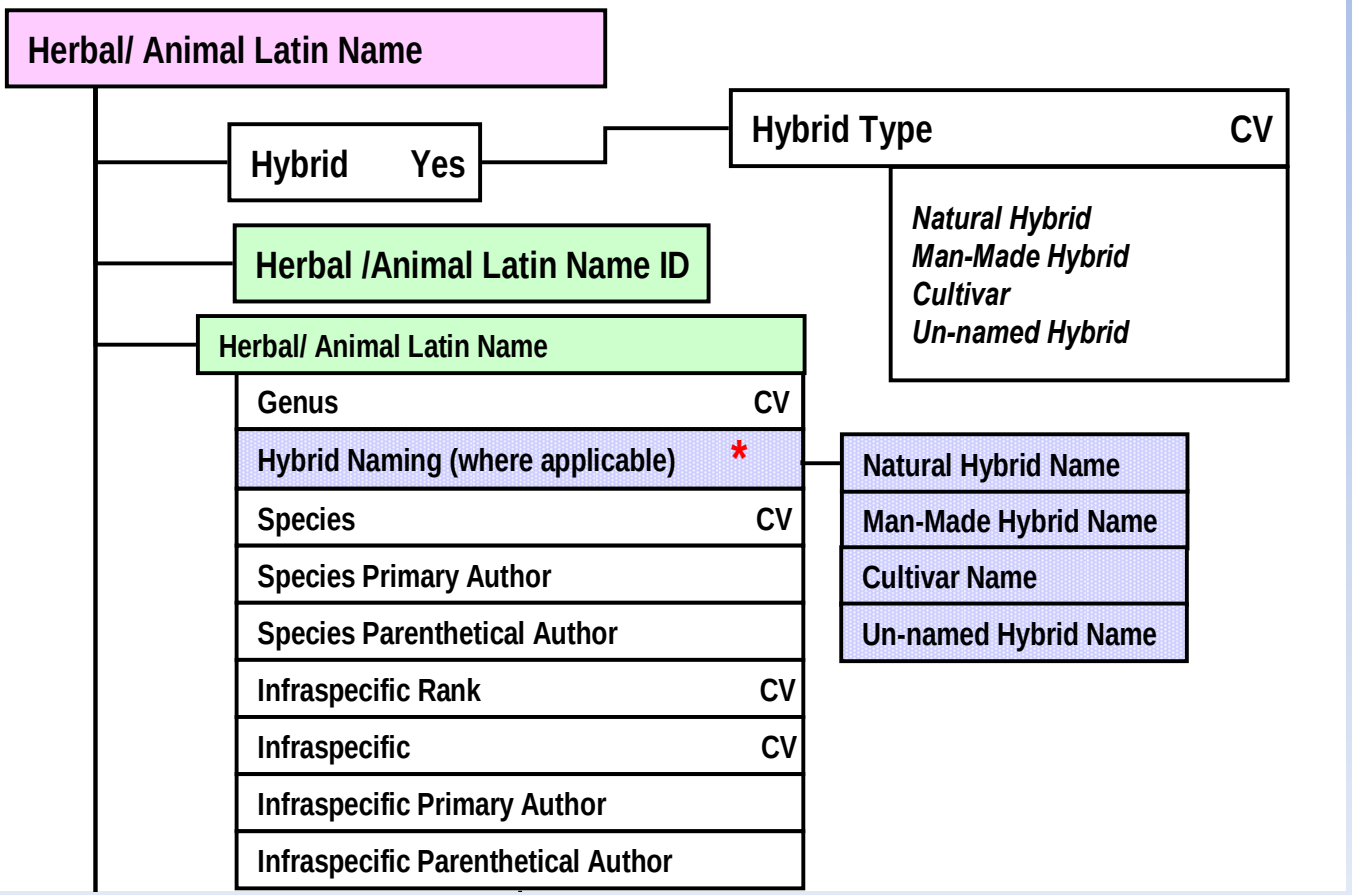
Class Source material Impl. Guide



ISO 11238 Standard (version 2009)



Important data elements for the unique identification the Herbal substance: Herbal Name



Herbal substance

- **Botanical name**
- Genus, Species, Author
- Family
- Common name
- Plant part used
- Growth state
- Description
- Marker
- Reference (*e.g Pharmacopoeia*)

Important data elements for the unique identification the Herbal substance, Name

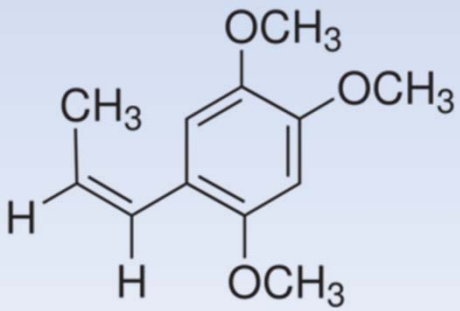
- **Botanical name** (incl. author and varieties)
- Hybrids / varieties/ cultivars?

β Asarone content of Acorus calamus varieties

var. *americanus* (Raf) Wulff (Diploid) Root (Rt) :ND, Essential oil (Eo): ND

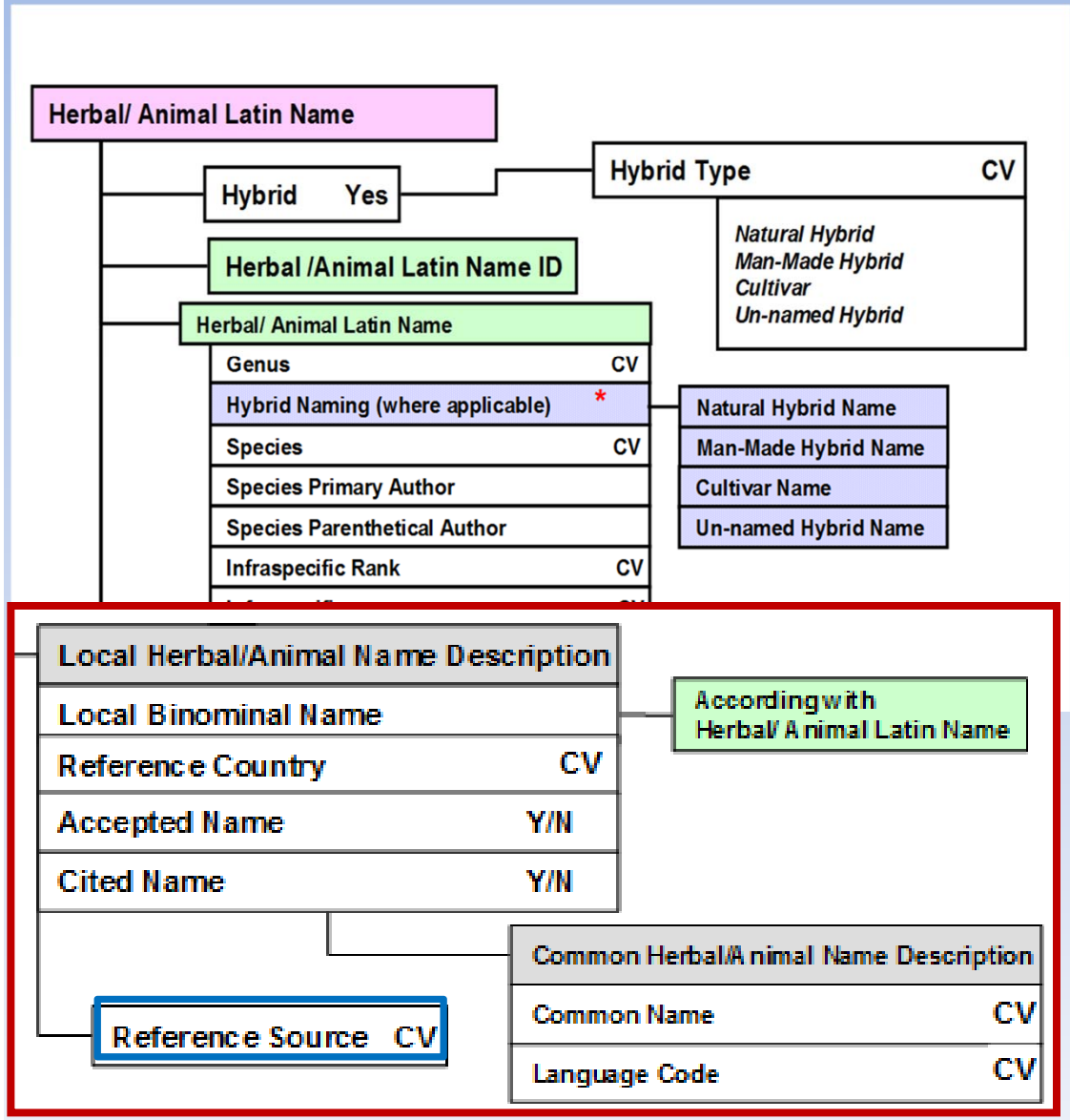
var. *calamus (triploid)* Rt: 0,3%, Eo:19%

var. *Angustatus (Bess) (tetraploid)* Rt: 8.3%, Eo: 95%



Beta-Asarone (**Cis-**2,4,5-trimethoxy-1-propenylbenzene**)** is found in several plants including *Acorus calamus* (family Araceae). The high percentage of the toxic substance (varying from 70 to 90% in tetraploid and hexaploid strains distributed extensively in India, Pakistan, Bangladesh, Japan, and China restricts the market potential of calamus oil.

Important data elements for the unique identification the Herbal substance: Name; *Origin and Common Name*



Fangji

(Aristolochia fangchi)

- More than 100 cases of nephropathia („Aristolochia nephropathia“)
- More 40 women are being dialysed.
- Cancer

(Stephania tetandra)

Important data elements for the unique identification the Herbal substance, *e.g.* Ginkgo Leaf

Herbal Substance: Ginkgo Leaf, Ginkgonis folium

Description: Whole or fragmented, dried leaf of Ginkgo biloba L.

Reference: European Pharmacopoiea

Genus: *Gingko*

Species: *biloba*

Author: L (linneaus)

Family: Ginkgoaceae

Common name: Gingko, Maidenhair tree

Plant part used: leaves

Growth state: before leaves turn yellow collected june to october

Processing: dried leaves

Marker : not less than 0.5 per cent of flavonoids, expressed as flavone glycoside

01/2011:1828

GINKGO LEAF

Ginkgonis folium

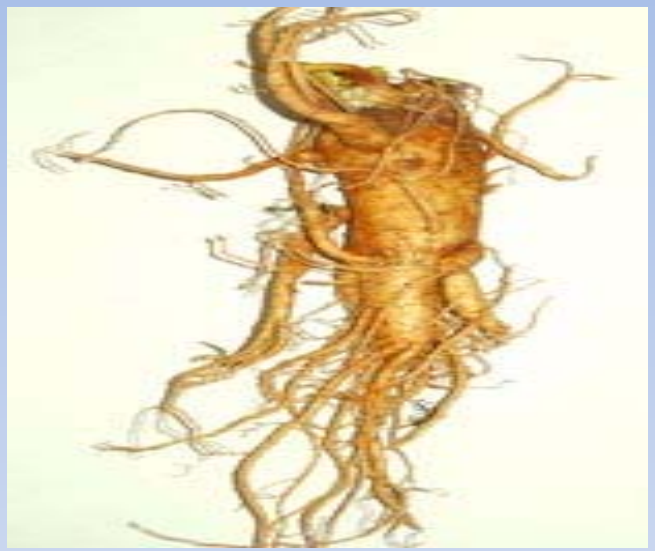
DEFINITION

Whole or fragmented, dried leaf of *Ginkgo biloba* L.

Content: not less than 0.5 per cent of flavonoids, expressed as flavone glycosides (M_r 757) (dried drug).

Herbal substance

Herbal Preparation



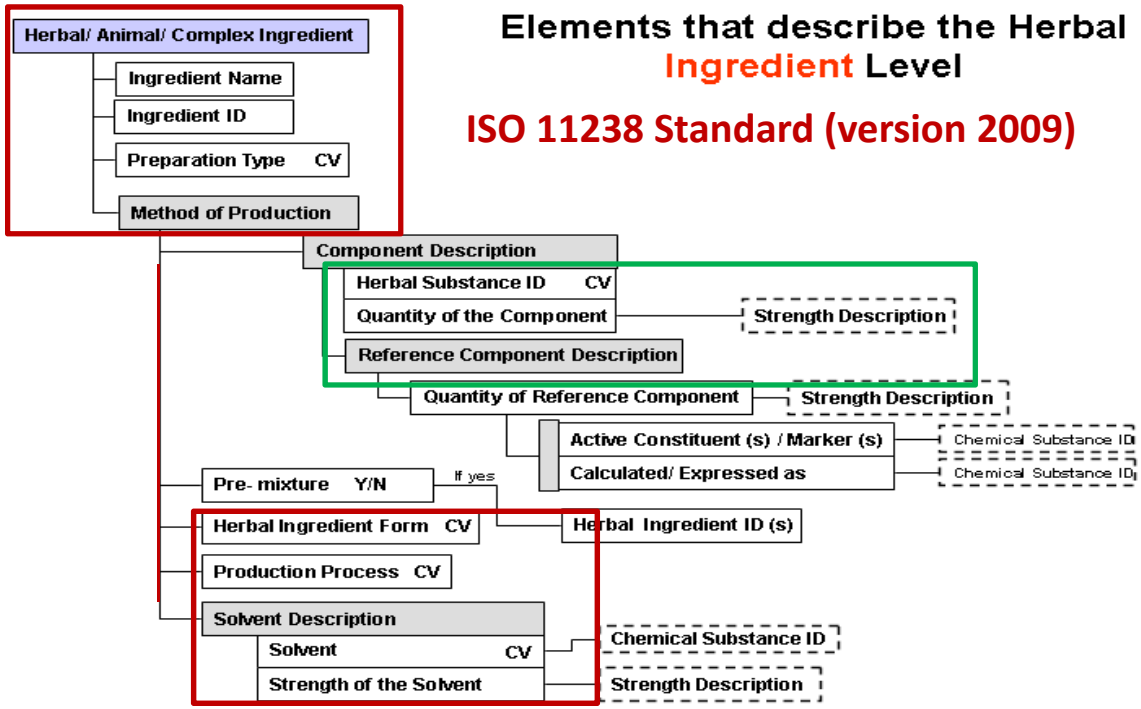
Herbal substance

Herbal preparation:

- Description
- DER
- Extraction solvent
- Manufacturing process
- Marker content

Herbal Preparation captured in the description of the ISO-11238 Standard, specified substance group 1 and 2

- **Group 1 Specified Substances:** Elements shall be used to describe material that contains multiple substances, *solvents used in the preparation of herbal* or allergenic extracts, *specific marker* or signature substances present in plant or animal derived materials, the physical form, any properties essential to the description of the material.
- **Group 2 Specified Substances** : Elements shall be used to *capture the manufacturer* of either a substance or a group 1 specified substance along with minimal manufacturing information. The minimal manufacturing information shall include the overall production method type, (i.e. synthetic, extractive, recombinant) production system type, (i.e. cell line, plant or animal tissue), production system (specific cell line).



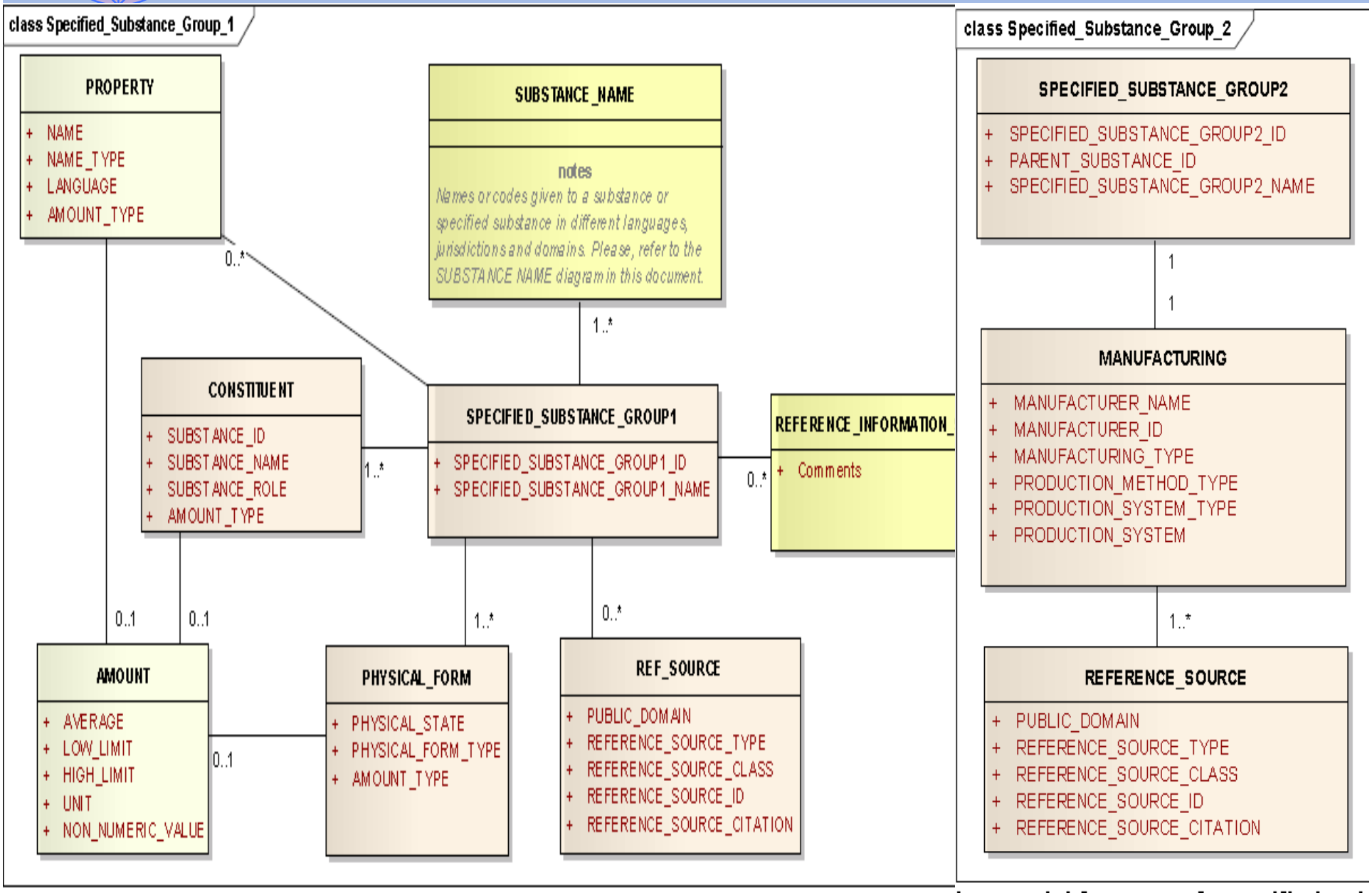
Elements that describe the Herbal Ingredient Level

ISO 11238 Standard (version 2009)

Herbal preparation:

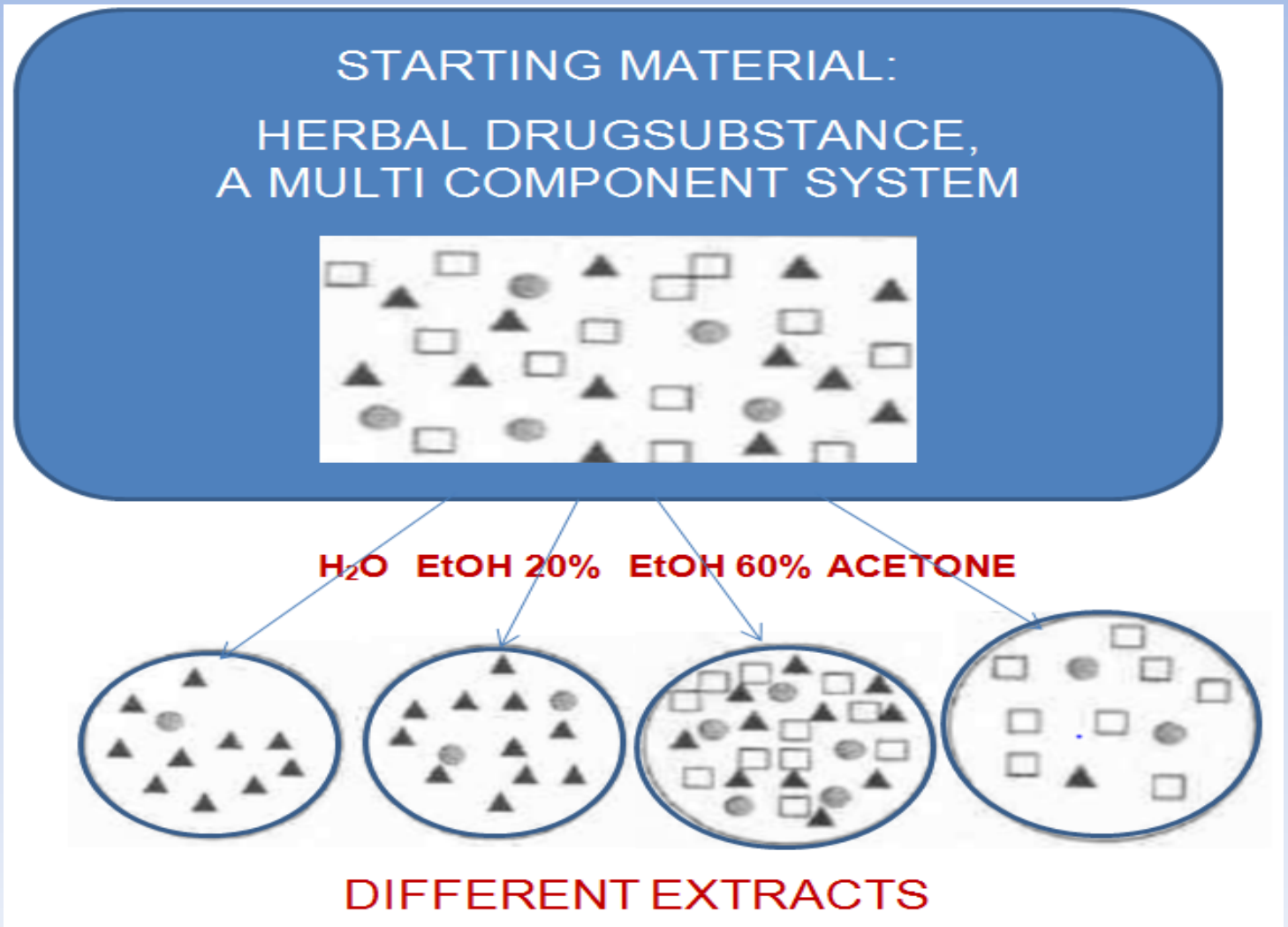
- Description
- DER
- Extraction solvent
- Manufacturing process
- Marker content

Overview IDMP ISO-11238 Information model
Specified Substance Group 1 and 2 (used for Herbal Preparation)



Important data elements for the unique identification the Herbal preparation *e.g. Solvent, DER, Amount Marker Content*

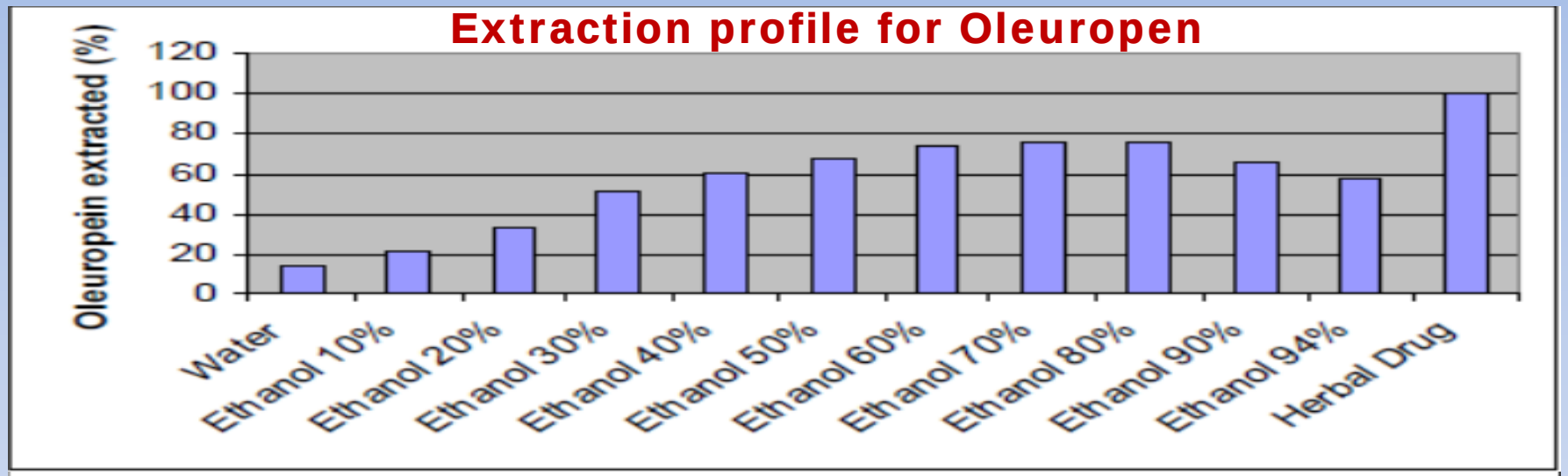
Composition and polarity of the extraction solvent or solvent mixture

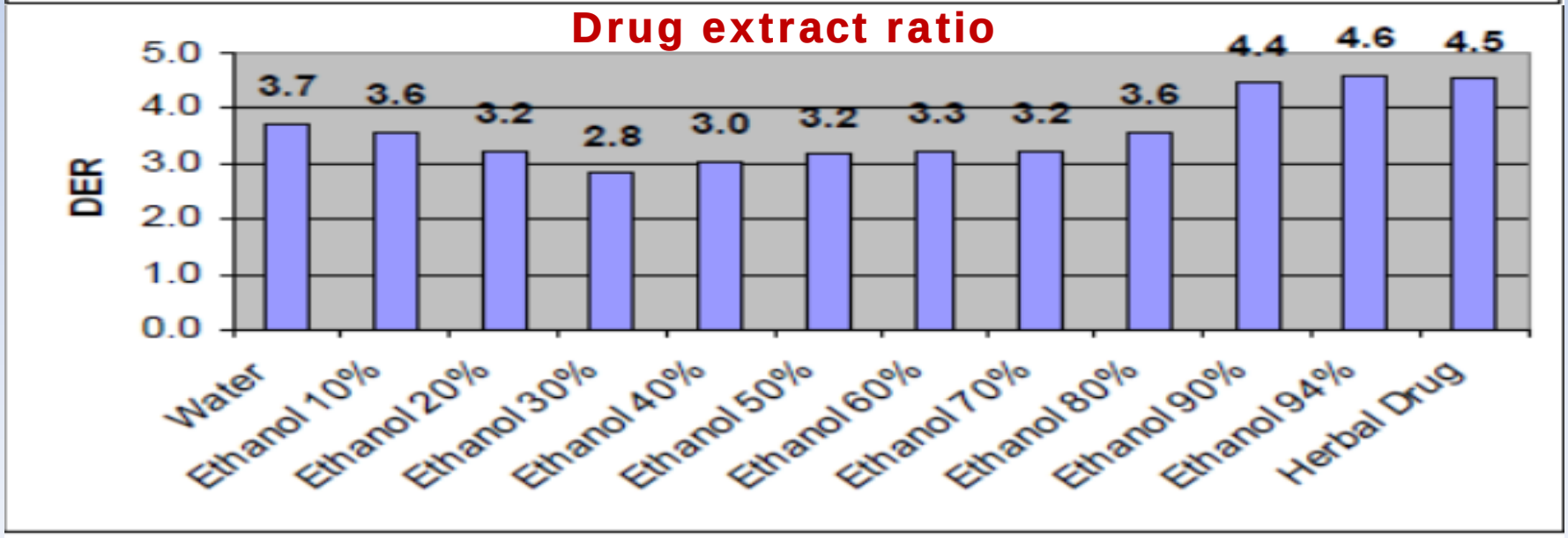


Important data elements for the unique identification the Herbal preparation *e.g. Solvent, DER, Amount Marker Content*

Selection of Drug Extract Ratio and Marker Gain related to the Solvent Comp. Range

Solvent composition Range: 65 – 96 pCt. v/v Ethanol





Important data elements for the unique identification the Herbal preparation *e.g.* Ginkgo extract, refined quantified

- **Description: 60 mg** dry refined acetone 60% extract, from Ginkgo biloba L., folium (35 – 67 : 1), corresponding to: 13.2 mg to 16.2 mg of **flavonoids** expressed as flavone glycosides, 1.68 mg to 2.04 mg of **ginkgolides A, B and C** and 1.56 mg to 1.92 mg of **bilobalide.**
- **Reference:** European Pharmacopoiea
- **Drug to Extract Ratio:** 35-67:1
- **Extraction solvent:** actone 60% in water. (first extract)
- Genuine extract content: 100%
- **Excipients:** Glycose Syrupe
- **Physical form:** dry
- **Marker content:**
  - flavonoids, expressed as flavone glycosides (Mr 756.7): 22.0 per cent to 27.0 per cent (dried extract);
  - bilobalide: 2.6 per cent to 3.2 per cent (dried extract);
  - ginkgolides A, B and C: 2.8 per cent to 3.4 per cent (dried extract);
  - **ginkgolic acids: maximum 5 ppm (dried extract)**

Herbal preparation:

- Description
- DER
- Extraction solvent
- Manufacturing process
- Marker content

Final blending:

Different lots dry extract are blended to adjust the content of the constituents in the final product according to the Ph. Eur.-monograph and include a quantity of dehydrated glycose syrup to standardize native extract in order to improve the quality

Declaration of herbal substances in the SmPC

The declaration of a herbal substance should cover the name and the quantity of the herbal substance.
The name is the scientific Latin name of the plant species according to the binomial system, etc.

EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1
Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/ traditional herbal medicinal products

The following characteristics have to be stated in the declaration:

1. Name of the herbal substance.
2. Quantity of the genuine herbal substance.
3. Name and quantity of the constituent(s) with known therapeutic activity (standardised herbal substances), if applicable.
4. Name and quantity (given as a range) of the active markers (quantified herbal substances), if applicable.

Declaration in section 2 of the SmPC of the herbal medicinal product:

Ginkgo dry extract, refined and quantified in tablets/ capsule/ oral drops

- ***Each tablet contains 40 mg of extract (as refined dry extract) from Ginkgo biloba L., folium (Ginkgo leaf) (35 – 67 :1), or:***
  Each tablet contains 40 mg of extract (as refined dry extract) from Ginkgo biloba l., folium (equivalent to 1.4 g – 2.7 g of Ginkgo leaf) , corresponding to:
- *22.0% -27.0 % (8.8 mg to 10.8 mg) of flavonoids calculated as flavone glycosides;*
  2.8% - 3.4% (1.12 mg – 1.36 mg) of ginkgolides A,B, and C;
  2.6% - 3.2% (1.04 mg – 1.28 mg) of bilobalide;
  and contains less than 5 ppm ginkgolic acids

Specification of the Ginko Extract

DETERMINATION	SPECIFICATION	U.m.
HPLC CONTENTS Flavonoids, expressed as flavone glycosides (determined on the dry native extract)	22.0 - 27.0	%
HPLC CONTENTS Biloballide (determined on the dry native extract)	2.6 - 3.2	%
HPLC CONTENTS Ginkgolides A,Band C (determined on the dry native extract)	2.8 - 3.4	%

1. Name of the medicinal product

<invented name 40 mg> film-coated tablets

Active substance: dry extract of Ginkgo biloba leaves

2. Qualitative and quantitative composition

1 film-coated tablet contains:
Active substance: 40 mg dry extract of Ginkgo biloba leaves (35-67:1), extractant: acetone 60% (m/m).
The extract is quantified to 22.0 - 27.0% flavonoids, calculated as flavonoid glycosides, as well as 2.6 - 3.2% bilobalide and 2.8 - 3.4% ginkgolides A, B and C, and contains less than 5 ppm ginkgolic acids per film-coated tablet.

For a full list of excipients, see section 6.1.

Detailed information and examples regarding the manufacturing procedure of the Herbal preparation in view of the depiction of the Specified Substance group 1 and 2 IDs

Examples of Herbal Substances and their Extraction Steps

- **One step extraction/ Maceration with 1 solvent composition and collection of both eluate and liquid from pressed residue** (most common procedure);
- **Multiple step extraction and enrichment (repeated extraction of the herbal substance) with the same solvent composition;**
- **One step extraction (with a solvent composition) and collection of the eluates of several perculators, and from pressed residue;**
- **Two step extraction with 2 solvent compositions with combining the eluates. The final eluate is concentrated to a liquid thick extract.**

- **These examples will demonstrate detailed information of the extraction/ manufacturing procedure that should be submitted and stored in the documentation of the database in order to appoint the unique specified substance identifier to the herbal preparation.**

Combined Extracts as Final Formulation of Medicinal Product

e.g. Iberogast, CBG-MEB database record

Iberogast--Steigerwald Arzneimittelwerk GmbH , RVG 103997

Ingredients to be discussed: **1) Angelica Radix; Liquiritiae Radix; Iberis amara (Iberogast)**

Title ▲ Iberogast, Liquid for Oral Use	Quant 1	Unit	Ingredient Type	
ANGELICA RADIX ETHANOLISCH (30 pCt.) EXTRACT (2,5-3,5 = 1) 0,1 = ml/ml	0,1	ml/ml	Actief bestanddeel	●
CARVI FRUCTUS ETHANOLISCH (30 pCt.) EXTRACT (2,5-3,5 = 1) 0,1 = ml/ml	0,1	ml/ml	Actief bestanddeel	
CHELIDONII HERBA ETHANOLISCH (30 pCt.) EXTRACT (2,5-3,5 = 1) 0,1 = ml/ml	0,1	ml/ml	Actief bestanddeel	
IBERIS AMARA ETHANOLISCH (50 pCt.) EXTRACT (1,5-2,5 = 1) 0,15 = ml/ml	0,15	ml/ml	Actief bestanddeel	●
LIQUIRITIAE RADIX ETHANOLISCH (30 pCt.) EXTRACT (2,5-3,5 = 1) 0,1 = ml/ml	0,1	ml/ml	Actief bestanddeel	●
MATRICARIAE CHAMOMILLAE FLOS ETHANOLISCH (30 pCt.) EXTRACT (2 - 4 = 1) 0,2 = ml/ml	0,2	ml/ml	Actief bestanddeel	
MELISSAE FOLIUM ETHANOLISCH (30 pCt.) EXTRACT (2,5-3,5 = 1) 0,1 = ml/ml	0,1	ml/ml	Actief bestanddeel	
MENTHAE PIPERITAE FOILIUM ETHANOLISCH (30 pCt.) EXTRACT (2,5-3,5 = 1) 0,05 = ml/ml	0,05	ml/ml	Actief bestanddeel	
SILYBI MARIANI FRUCTUS ETHANOLISCH (30 pCt.) EXTRACT (2,5 - 3,5 = 1) 0,1 = ml/ml	0,1	ml/ml	Actief bestanddeel	

Selection is chosen based on the type of extraction procedure of the herbal substance:

(Manufacturing of the Herbal preparation)

Angelica Radix: One step extraction/ Maceration with 1 solvent composition and collection of both eluate and liquid from pressed residue. Filtering after 14 days of storage.

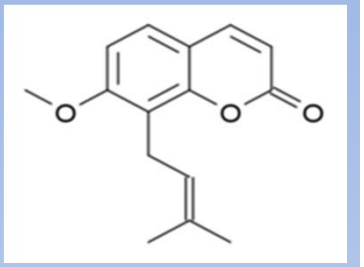
Liquiritiae Radix: Multiple step extraction and enrichment (repeated extraction of the herbal substance) with 1 solvent composition. Filtering after 14 days of storage .

Iberis amara: One step extraction with 1 solvent composition and collection of the eluates of several perculators, and from pressed residue. Filtering after 14 days of storage.

2) Traditional Herbal Medicinal Product Danshen Capsule: Salvia militiorrhiza Rhizoma, (Chin. FDA)

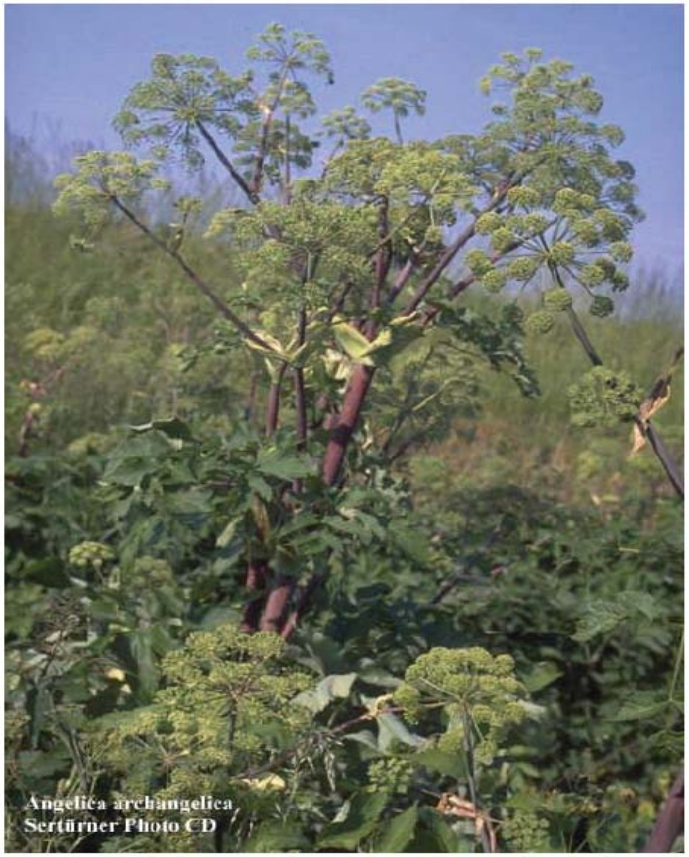
Salvia militiorrhiza Rhizoma: Two step extraction with 2 solvent compositions with combining the eluates. The final eluate is concentrated to a liquid thick extract. (*Extractum liquidum spissum*)

Combined Extracts as Final Formulation of the Medicinal Product, e.g. Iberogast



Herbal Substance:

Scientific Name: Angelica archangelica L. (Angelica *officinalis* Hoffm.)
Parts of the plant: Dried Rhizome and Root, Cut pieces of 4 – 6 mm.
Supplier of Herbal Substance: *e.g.* Agrimed Hessen w.V., Trebur, Germany
Harvest time, **Cultivated plants**: June – August, Germany and Eastern Europe
Marker Substance: Coumarin [7-Methoxy-8-(3-methyl-2-butenyl)-2*H*-1-benzopyran-2-one] *"Osthole"*



EP Monograph no. 1857 01/2013:1857

ANGELICA ARCHANGELICA ROOT

Angelicae archangelicae radix

DEFINITION

Whole or cut, carefully dried rhizome and root of *Angelica archangelica* L. (syn. *A. officinalis* Hoffm.).

Content: minimum 2.0 mL/kg of essential oil (dried drug).

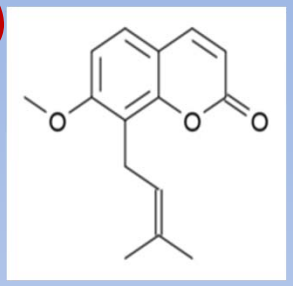
CHARACTERS

Bitter taste.

IDENTIFICATION

A. The rhizome is greyish-brown or reddish-brown, with transversely annulated thickenings. The base bears greyish-brown or reddish-brown, cylindrical, longitudinally furrowed, occasionally branched roots often with incompletely encircling, transverse ridges. The apex sometimes shows remnants of stem and leaf bases. The fracture is uneven. The transversely cut surface shows a greyish-white, spongy, distinctly radiate bark, in which the secretory channels are visible as brown spots, and a bright yellow or greyish-yellow wood which, in the rhizome, surrounds the greyish or brownish-white pith.

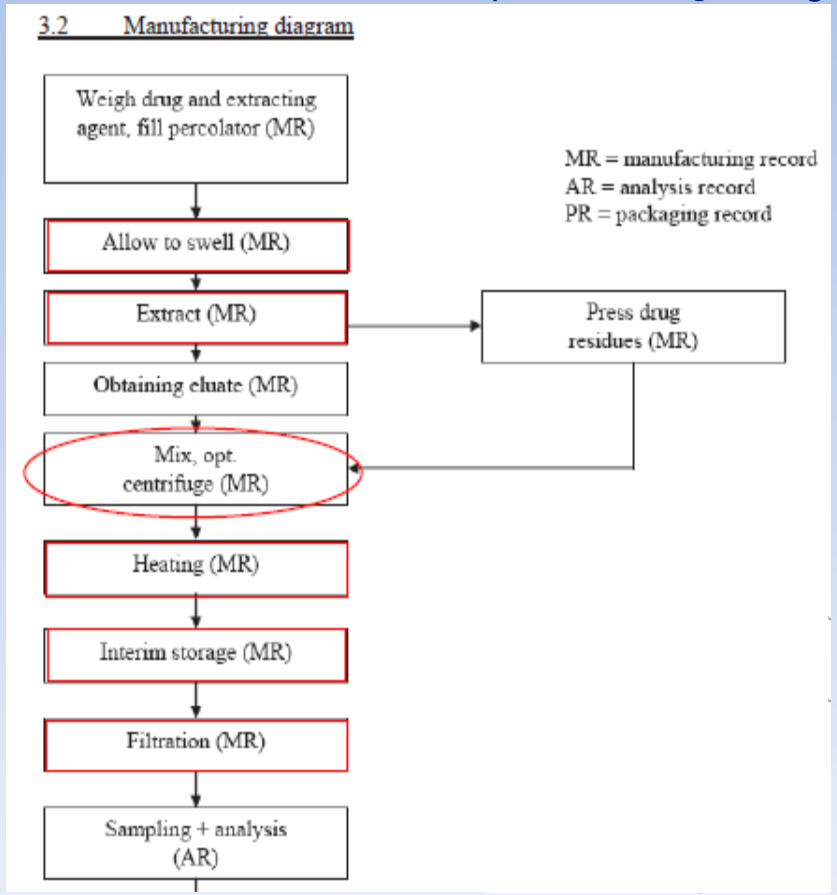
Combined Extracts as Final Formulation of the Medicinal Product, e.g. Iberogast *(Cont., Angelica Radix Extr.)*



Herbal Preparation:

Extract: Ethanolic 30 pCt –water extract of angelica root (2,5 – 3,5 =1);
Dutch Name: Angelica Radix Ethanolisch (30 pCt.) Extract (2,5 – 3,5 = 1);
DER: 2,5 – 3,5 Parts Herbal Substance = 1,0 Part Extract;
Extraction solvent: Ethanol (30) – Water (70) = Ethanol 30 pCt.
Manufacturer of Herbal Preparation: *e.g.* Steigerwald Arzneimittelwerk GmbH, Germany

*"**Osthole**"*



Manufacturing Process:

- **Swelling** of the Plant material with Ethanol 30 pCt. at 20°C for 12 hours.
- **Extraction** for 6 hours at of 20°C. Residual Plant material is pressed and discarded. The eluents are combined and heated at 50°C for 15 min. (Pasteurization)
- **Storage of the extract** for at >= 14 days at 20°C before filtration. The final extract is stored until further processing in the Herbal Product.
- **The strength** of the Final Extract is based on the **marker concentration in the extract.** (*Spec: 0,05 – 0,15 mg/ml **Osthole,** Cas. No. 484-12-8,* Mol. Form.: C15 H16 O3; Mol. Weight: 244,3 g/mol.*)*

Combined Extracts as Final Formulation of the Medicinal Product, e.g. Iberogast *(Continued)*

Herbal Substance:

Scientific Name: Glycyrrhiza glabra L. (Fabaceae)

Parts of the plant: Dried, Peeled Root and Stolons, Cut pieces of 4 – 6 mm.

Supplier of Herbal Substance: *e.g.* Martin Bauer GmbH & Co. KG , Germany.

Harvest time, Wild & Cultivated plants: April-September, Asia (wild) and Europe (cultivated).

Marker Substance: **Glycyrrhizic acid** (CAS NO.: 1405-86-3; Mol. Form.: C42 H62 O16; Mol. Weight: 822,94 Da)

LIQUORICE ROOT

Liquiritiae radix

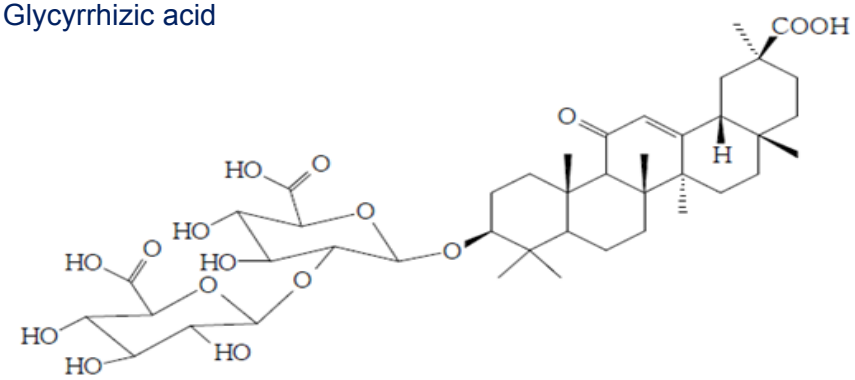
DEFINITION

Dried, unpeeled or peeled, whole or cut root and stolons of *Glycyrrhiza glabra* L. and/or of *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch.

Content: minimum 4.0 per cent of 18β-glycyrrhizic acid ($C_{42}H_{62}O_{16}$; M_r 823) (dried drug).

EP monograph no. 277

Glycyrrhizic acid



IUPAC-name: 20β-Carboxy-11-oxo-30-norolean-12-en-3β-yl-2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid.

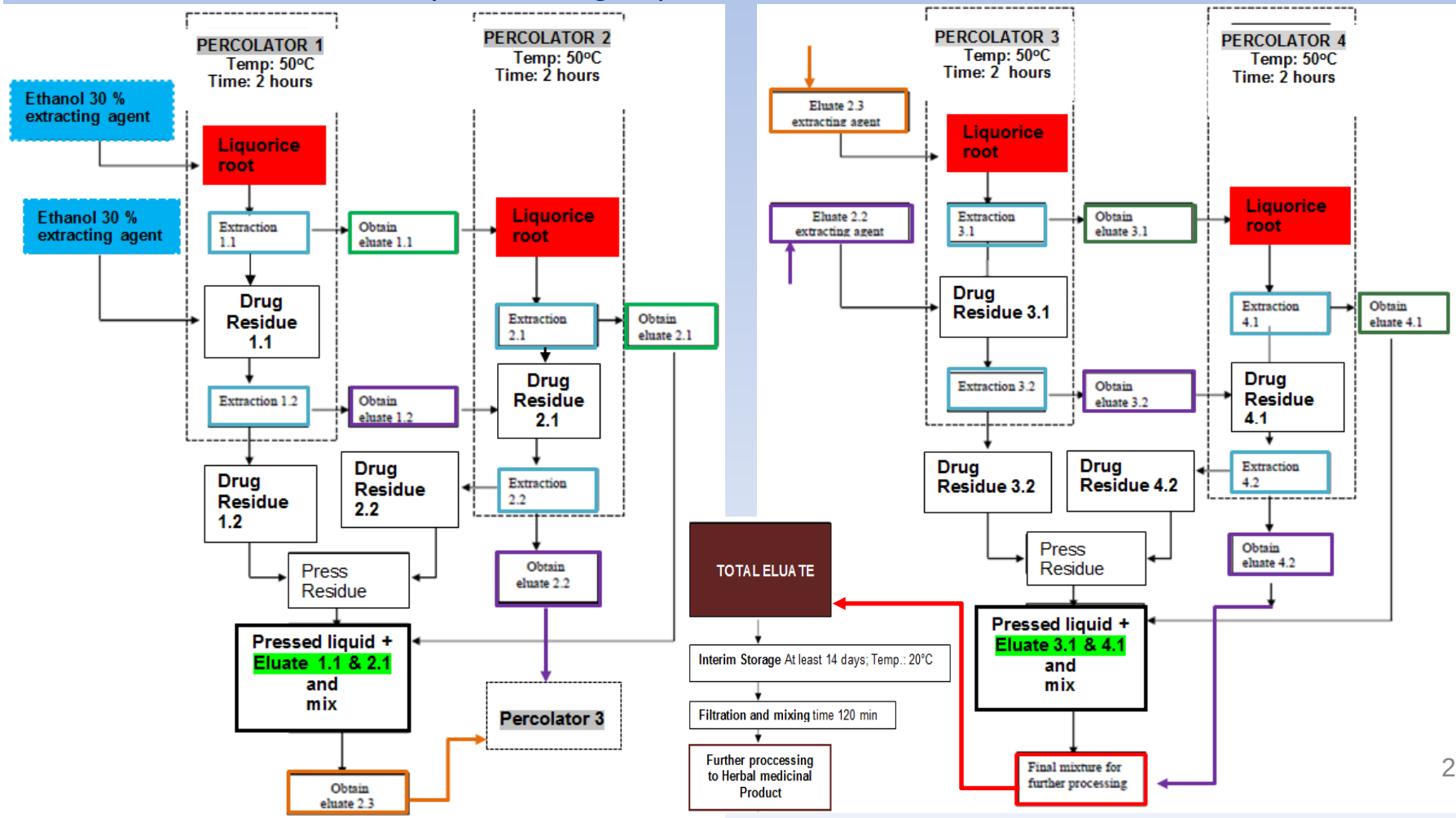
Constituents: glycosides called glycyrrhizin (7%) and glycyrrhizinic acid, triterpenoid glycosides (saponins), flavonoids and isoflavonoids, bitter principle (glycyrmarin), volatile oil, chalcones, coumarins, amino acids, amines (choline, betaine, asparagine), oestrogenic substances (including beta-sitosterol), glucose and sucrose (5-15% sugars), starch, tannins, gums, wax.

Combined Extracts as Final Formulation of the Medicinal Product, e.g. Iberogast *(Cont. Liquiritiae Radix Extr.)*

Herbal Preparation:

Extract: Ethanolic 30 pCt –water extract of liquorice root (2,5 – 3,5 = 1);
Dutch Name: Liquiritiae Radix Ethanolisch(30 pCt.) Extract (2,5-3,5 = 1);
DER: 2,5 – 3,5 Parts Herbal Substance = 1,0 Part Extract;
Extraction solvent: Ethanol (30) – Water (70) = Ethanol 30 pCt.
Manufacturer of Herbal Preparation: *e.g.* Alpinamed AG, Switserland

The strength of the Final Extract is based on the **marker concentration in the extract:** 7 -12 mg/ml glycyrrhizic acid**.**



Combined Extracts as Final Formulation of the Medicinal Product, e.g. Iberogast *(Continued)*

Herbal Substance:

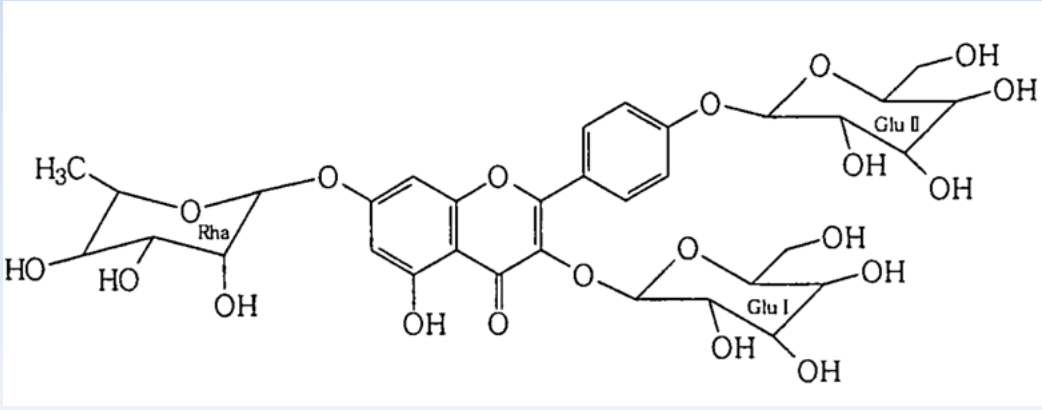
Scientific Name: Iberis amara L., Iberis amara totalis (Brassicaceae)
Parts of the plant: Fresh whole plant.
Supplier of Herbal Substance: *e.g.* Agrimed Hessen, Germany.
Harvest time, Cultivated plants: June-August, Germany; shock frozen directly after harvesting.
Storage condition: Protected from light at Temp. -20°C to - 24°C for max. 24 months.
Marker Substance: Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-rhamnopyranoside

English name: Bitter candytuft;

Iberis amara L. is an annual, white blooming plant, reaching up to 40 cm of heights with a strong specific smell, and a bitter cress-like taste. The flowers contain a wealth of flavonol glycosides of the kaempferoltype.

IUPAC name:
Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-rhamnopyranoside.

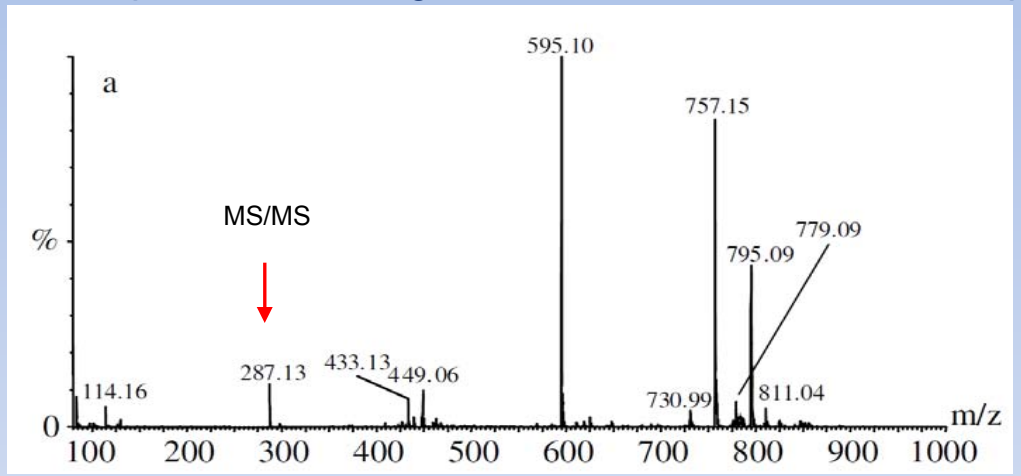
Mol. Form.: C33 H44 O20
Mol. Weight: 756,38 Da



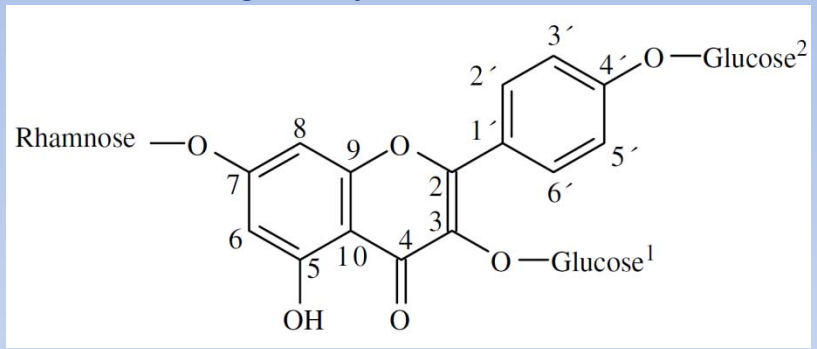
Combined Extracts as Final Formulation of the Medicinal Product, e.g. Iberogast *(Continued)*

Structure elucidation Marker substance (HPLC ESI-MS and MS/MS-spectra):

English name: Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-rhamnopyranoside
IUPAC: Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-rhamnopyranoside
Synonyms: Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-L-rhamnopyranoside: Kaempferol-3,4' -O-diglucoside-7-O-rhamnoside; Kaempferol-3,4´-O-diglucosyl-7-O-rhamnoside.

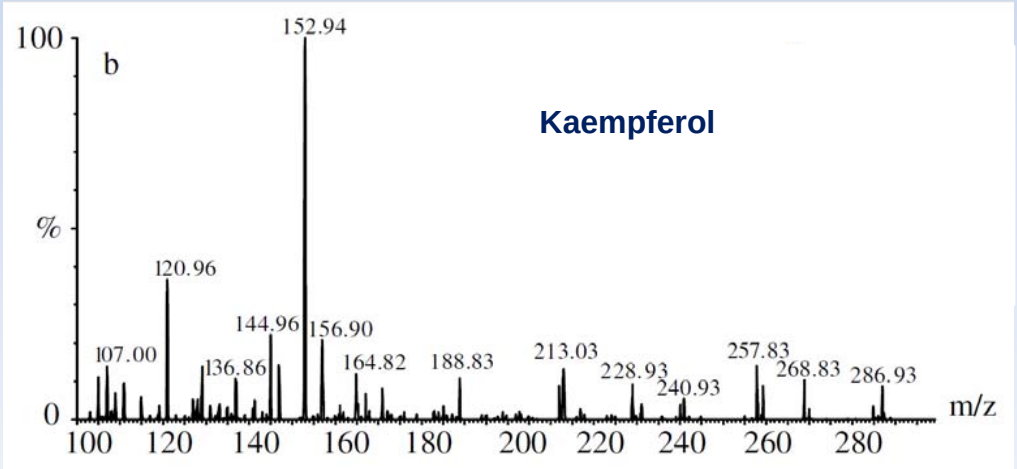


a) MS-spectrum of Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-rhamnopyranoside



Mol. Form.: C33 H40 O20; Mol. Weight: 756 Da

[M+H]$^{+}$= 757 m/z
[M+H-162] = 595 m/z (-/- Glucose^{2})
[M+H-162-146] = 449 m/z (-/- Rhamnose)
[M+H-2x162]= 433 m/z (-/- Glucose^{1+2})
[M+H-2x162-146]=287 m/z (= Kaempferol)

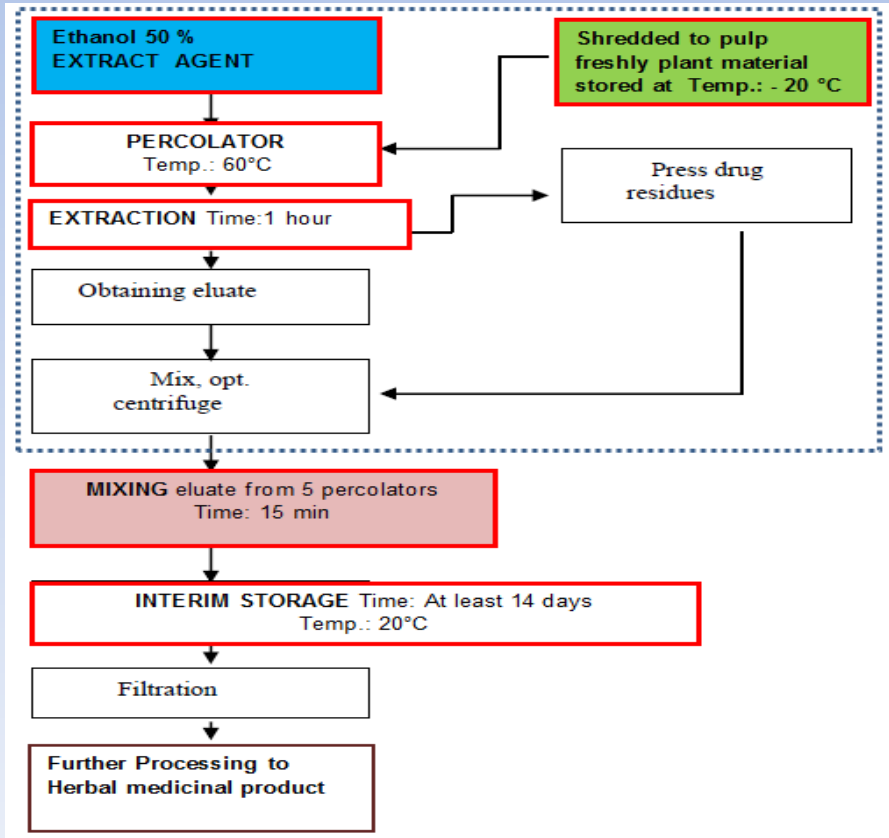


b) MS/MS-spectrum of **ion 287 m/z** of Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-rhamnopyranoside

Combined Extracts as Final Formulation of the Medicinal Product, e.g. Iberogast *(Cont. Iberis amara Extr.)*

Herbal Preparation:

Extract: Ethanolic 50 pCt–water extract of fresh plants of bitter candytuft (1,5 – 2,5 = 1);
Dutch Name: Iberis Amara Ethanolisch (50 pCt.) Extract (1,5-2,5 = 1);
Degree of comminution: Whole plant, shredded to pulp prior to extraction.
DER: 1,5 – 2,5 Parts Herbal Substance = 1,0 Part Extract;
Extraction solvent: Ethanol (50) – Water (50) = Ethanol 50 pCt.
Manufacturer of Herbal Preparation: *e.g.* Steigerwald Arzneimittelwerk GmbH, Germany



Manufacturing Proces:

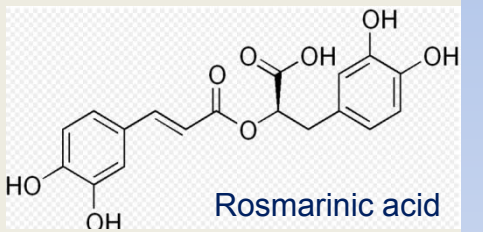
Extraction for 1 hour at of 60°C. Residual plant material is pressed and discarded. The eluates are combined.
The total eluates from the 5 percolators are combined and mixed for 15 min..

Storage of the extract for at >= 14 days at 20°C before filtration. The final extract is stored until further processing in the Herbal Product.

The strength of the Final Extract is based on the **marker concentration in the extract.**
(*Spec: 0,05 – 0,15 mg/ml* ***Kaempferol-3,4' -O-β-diglucopyranoside-7-O-α-rhamnopyranoside***
Mol. Form.: C33 H44 O20;
Mol. Weight: 756,38 g/mol.)

Formulation of a Traditional Herbal Medicinal Product, e.g. Danshen Capsule

Herbal Substance: [Nomenclature based on the CFDA (China Food and Drug Administration)]
Scientific Name: **Salvia miltiorrhiza Bunge**; Family: *Labiatae* (Lamiaceae)
Parts of the plant: Dried, fragmented root and rhizome, cut pieces NMT 5 cm.
Supplier of Herbal Substance: *e.g.* Tasly Plant Pharmaceutical, Shaanxi province, China
Harvest time, **Cultivated plants**: In the autumn of the next year after seeding when the aerial parts of the plants are wilting (Shaanxi province of China). The harvested material is dried at 50°C – 60°C as soon as possible after harvesting (loss on drying ≤13%) and stored in closed PP bags under low relative humidity conditions.
Marker Substance for specification:
- Salvianolic acid B (Mol. Form.: C36 H30 O16; Mol. Weight: 718,6 Da); NLT 3,0 %
- Tanshinone IIA (Mol. Form.: C19 H18 O3; Mol. Weight: 294,3 Da) ; NLT 0,12 %
Analytical marker: Rosmarinic acid (Mol. Form.: C18 H16 O8; Mol. Weight: 360,3 Da); BP-spec.:NLT 0,17 %



Rosmarinic acid

CAS Registry Name:
Benzenepropanoic acid, .alpha.-[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-3,4-dihydroxy-, (.alpha.R)-
CAS No.: 20283-92-5

Salvia miltiorrhiza, also known as red sage, tan shen, or danshen, is a perennial plant of the genus Salvia, highly valued for its roots in traditional Chinese medicine.

Native to China and Japan, it grows at 90 to 1,200 m (300 to 3,900 ft) elevation, preferring grassy places in forests, hillsides, and along stream banks.

Sample of the Root and Rhizoma. Cylindrical, slightly curved segments, 5 cm long. The external surface is reddish brown, rough with longitudinal striations.

SALVIA MILTIORRHIZA ROOT AND RHIZOME

Salviae miltiorrhizae radix et rhizoma

DEFINITION

Dried, whole or fragmented rhizome and root of *Salvia miltiorrhiza* Bunge, collected in spring or autumn.

Content:

- *salvianolic acid B* ($C_{36}H_{30}O_{16}$; M_r 719): minimum 3.0 per cent (dried drug);
- *tanshinone II_A* ($C_{19}H_{18}O_3$; M_r 294.3): minimum 0.12 per cent (dried drug).

EP monograph no.: 2663

Formulation of a Traditional Herbal Medicinal Product, e.g. Danshen Capsule (*Cont. Salvia miltiorrhiza Radix Extr.)*)

Herbal Preparation:

Extract: Danshen extract is a brown to dark brown soft (semi-solid) extract, made through the process of extraction and concentration (4,5 – 6 = 1).

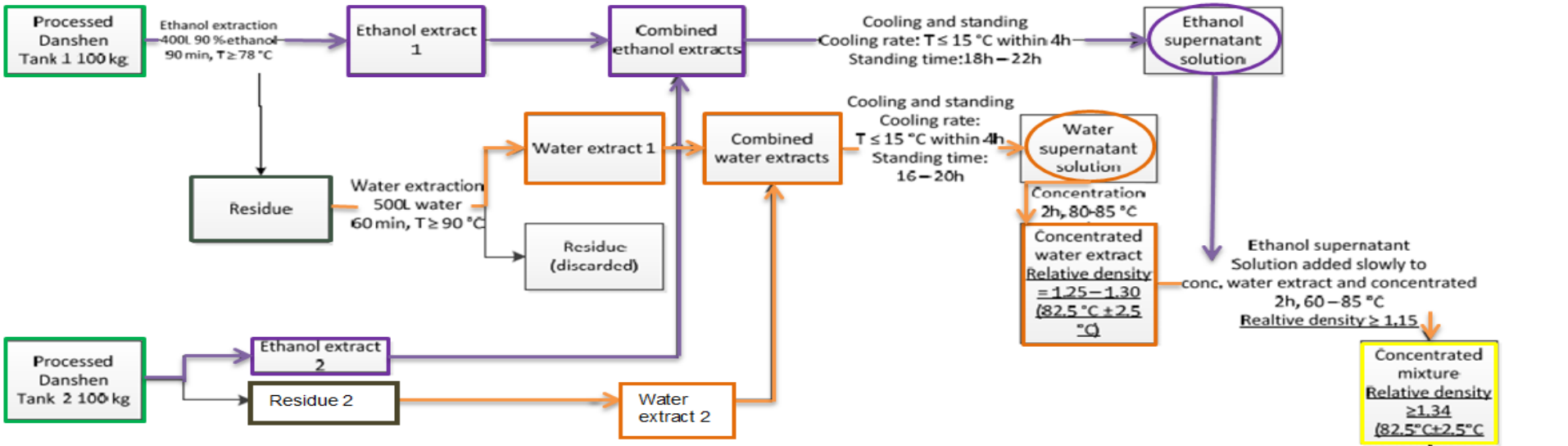
Name: Salvia miltiorrhiza root and rhizome Ethanolic (90 pCt.)-water liquid extract (4,5 – 6 = 1).

Dutch Name: Salvia miltiorrhiza wortel en wortelstok ethanolisch (90 pCt.) en waterig droog extract (4,5 – 6 = 1);

DER: 4,5 – 6 Parts Herbal Substance = 1,0 Part Extract;

Extraction solvent: Ethanol (90) – Water (10) = Ethanol 90 pCt.

Manufacturer of Herbal Preparation: *e.g.* Tasly Pharmaceutical Group Co., Ltd, China



1) **Extraction:** Ethanol 90 % extraction for 90 min at of 78°C, Residual plant material is extracted with 100 % water for 60 minutes at 90°C.
2) **Cooling and decantation:** The ethanol and water extract are collected in separate tanks and stirred for 30 minutes, cooled to 15°C and then allowed to stand for 18-22 hours and 16-20 hours for the ethanol and water extracts, respectively.
3) **Concentration:** The water supernatant is concentrated for about 2 hours at 80°C under reduced pressure.
4) **Mixing and concentration: The Ethanol supernatant and concentrated water extract are combined and further concentrated to a specified relative density.** Content of rosmarinic acid: NLT 1,86 mg/g

Thank you for your attention

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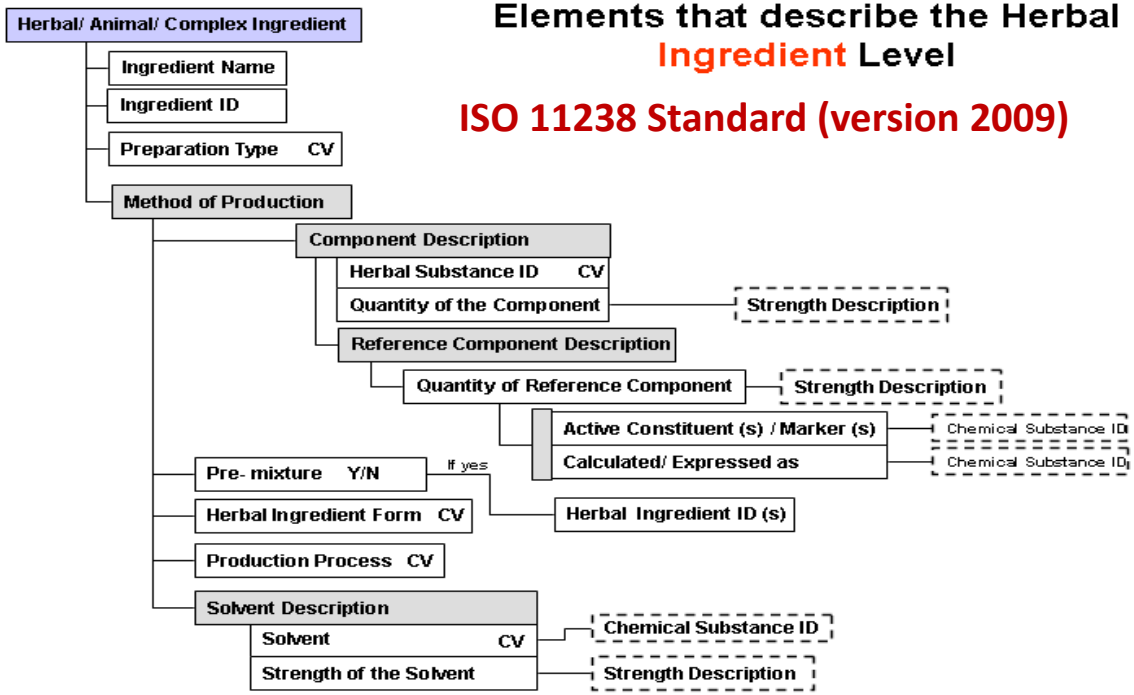
Back Up

Herbal Preparation captured in the description of the ISO-11238 Standard, specified substance group 1 and 2

- **Group 1 Specified Substances:** **Elements shall be used to describe material that contains multiple substances, solvents used in the preparation of herbal or allergenic extracts, specific marker or signature substances present in plant or animal derived materials, the physical form, any properties essential to the description of the material.**
- **Group 2 Specified Substances** : **Elements shall be used to capture the manufacturer of either a substance or a group 1 specified substance along with minimal manufacturing information. The minimal manufacturing information shall include the overall production method type,** (i.e. synthetic, extractive, recombinant) production system type, (i.e. cell line, plant or animal tissue), production system (specific cell line).



Herbal preparation:

- Description
- DER
- Extraction solvent
- Manufacturing process
- Marker content