

EDQM Symposium

Herbal Drugs & Herbal Drug Preparations

25 September 2009
Vienna, Austria



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Third Session

Update on recent discussions & developments



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Reference Standards for Herbal Drugs and Herbal Drug Preparations



Symposium Vienna
September 2009
Ulrich Rose, EDQM



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Content of the presentation

- Definitions and guidelines
- Types of standards
- Use in a pharmacopoeial monograph
- Examples
- Establishment and value assignment
- Conclusion



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Classification

- CRS ---- BRP ---- HRS
 - CRS: Chemical reference substance
 - BRP: Biological reference preparation
 - HRS: Herbal reference standard
- Primary standards - secondary standards
- Classification according to purpose:
 - Identification, Test for related substances, Assay

Definitions and Guidelines (5.12.)

- Required to achieve adequate quality control of substances for pharmaceutical use and pharmaceutical preparations
- A Ph. Eur. reference standard is an integral part of a pharmacopoeial monograph and represents the official standard that is alone authoritative in case of doubt or dispute

Definitions and Guidelines (2)

- General Chapter 5. 12.
- Reference Standards (Ph. Eur. 5.6)
- **European Pharmacopoeia Chemical Reference Substance (CRS) :**
- «A substance or mixture of substances intended for use as stated in a monograph or general chapter of the European Pharmacopoeia. European Pharmacopoeia CRS are primary standards, except for those (notably antibiotics) that are calibrated in International Units. The latter are secondary standards traceable to the international standard ».

Definitions and Guidelines (3)

- General Chapter 5.12
- *Assay of components of herbal drugs and herbal drug preparations:*
 - An active component or marker constituent is characterised and evaluated for identity and purity; a value of content is assigned irrespective of the purity.
 - An extract is used as reference standard when insufficient active principle or marker constituent is available. The assigned content of the extract is established by means of a collaborative trial using a well-characterised sample of the active principle or marker component for which a value is to be assigned.

Reference standards for monographs on herbal drugs and preparations

- Types of reference standards:
 - Active principle (single compound)
 - Active or inactive marker (single compound)
 - Herbal extract (extract with assigned content for one or more components, HRS)
 - Herbal drug (HRS)



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Reference standards for monographs on herbal drugs and preparations

- Use:
 - Qualitative use: peak identification and system suitability test
 - Quantitative use: assay standard with assigned content



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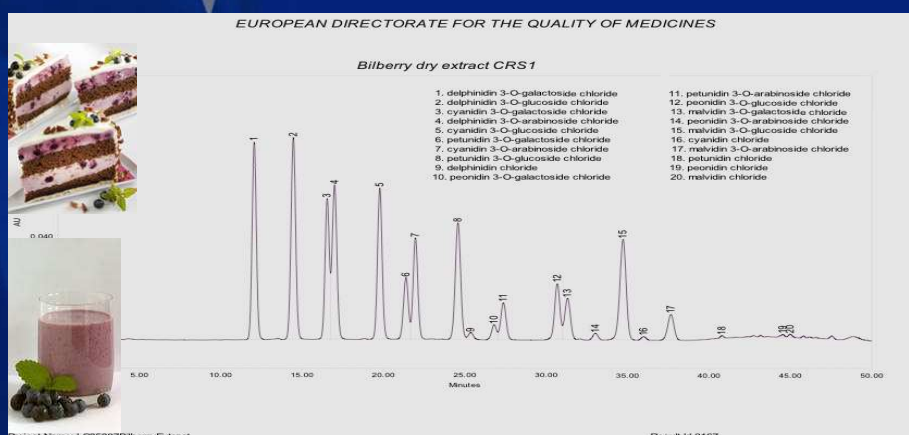
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Reference standards for monographs on herbal drugs and preparations (2)

- Qualitative use: **Bilberry dry extract CRS**
- - LC-test for total anthocyanidins
- - Identification of peaks due to anthocyanins and anthocyanidins
- System suitability test: peak-to-valley ratio between cyanidin 3-O-galactoside (peak 3) and delphinidin 3-O-arabinoside (peak 4)
- LC – assay of total anthocyanins



Reference standards for monographs on herbal drugs and preparations (3)



Reference standards for monographs on herbal drugs and preparations (2)

- Quantitative use:
 - Active ingredients or marker substances
 - Herbal extracts with assigned content of active ingredient or marker

Active ingredients or marker substances

- Boldine, Coumarin, Ruscogenins, Chlorogenic acid, Verbenaline, Harpagoside, Salicin, Capsaicin, Nonivamide, Oleuropein, Aescin, Rosmarinic acid, Morphine HCl, Quercetine dihydrate, Ferulic acid, Olein, Cyanidin chloride, Santonin, Benzanilide, Rutoside trihydrate, Resveratrol, Aristolochic acid, Piperine, Tetrandrine, Berberine chloride, Hydrastine HCl, Brucine, Strychnine....

Establishment of single compounds (CRS)

1. Structural identification
2. Purity, usually by HPLC
3. Loss on drying, TGA
4. Residual solvents
5. Absolute methods like titration, DSC, quantitative NMR
6. *The use of a marker may require the establishment of a **response factor** (e. g. acteoside – ferulic acid CRS in Lemon verbena leaf)*

Establishment of single compounds (CRS)

- **Assignment of content**
- For standards used in physico-chemical assays:
 - Declaration of content on an « as is » basis:
 - $X (\%) = (100 - \text{water/solvents}) \times \text{chromatographic purity}/100$
 - Lyophilised standards
 - Exact quantity per vial is assigned (mg/vial)
 - Examples: Harpagoside CRS 1: 1.03 mg/vial
 - Verbenalin CRS 1: 0.97 mg/vial

Herbal extracts (1)

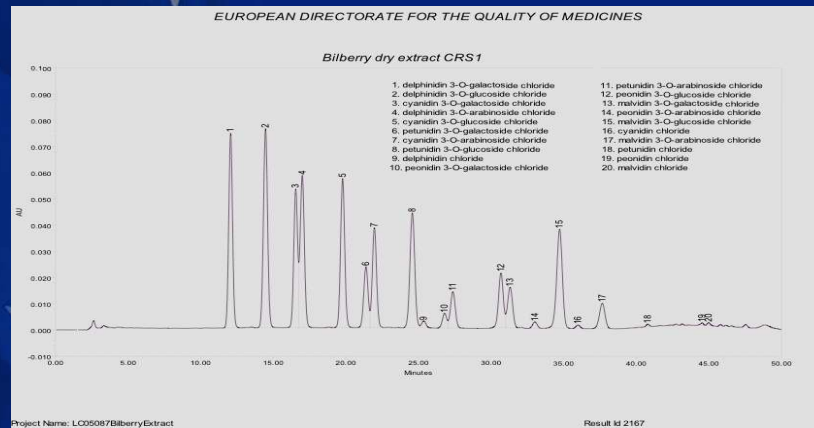
- Option chosen when the « active principle » or marker substance are not available in sufficient amounts or instable in isolated form:
- Valerian dry extract
- Ivy leaf tincture
- Agnus Castus fruit dry extract
- Bilberry dry extract
- St. John's Wort dry extract
- Milk thistle dry extract
- Ginkgolic acids
- and others...

Herbal extracts (2)

- A well characterised sample of the « active principle » is used as external standard
- Characterisation:
 - Structural identification
 - Purity tests
 - Solvent analysis
 - Determination of content of « active principle » in the extract in a collaborative trial

Herbal extracts (3)

Assay: Total anthocyanins expressed as cyanidin 3-O-glucoside, assigned content 3.44 %



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Recent Developments

Use of powdered herbals drugs as reference standards (HRS)

- Equisetum palustre: test for adulterations by TLC in the monograph for equisetum stem
- Long pepper: peak identification and system suitability test in monograph for long pepper
- Aristolochia serpentaria: Screening test for aristolochic acids by TLC



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Monitoring (retest-programme)

- After establishment and adoption there is a standardised testing procedure in order to assure the « fitness for use » of the reference standards.
- Depending on the use and the known or predicted stability, substances are retested every 12, 24, 36 or 60 months
- Items of retesting: All properties which are subject to change in a life cycle of a CRS, i. e.:
- Water content
- Purity by HPLC, GC or TLC
- Possibly IR, UV



For comparison: International prototype kilogram

in Sèvres, monitored every 40 years

Conclusion

- Primary standards
- CRS and HRS
- Way of establishment is use-dependent
- Use for the intended purpose (qualitative and/or quantitative)
- Essential requirement: suitable for the intended purpose
- Retesting instead of expiry dates

Thank you for your attention



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Characterisation of constituents by group determinations – a pragmatic approach for herbal drugs and herbal drug preparations

Dr. Anton Biber, Deutsche Homöopathie-Union GmbH & Co. KG, Karlsruhe
25 September 2009, Vienna



Quality of herbal drugs/preparations...

- herbal drugs/preparations are essentially defined by their production process and their specifications
- specification is defined as a list of analytical procedures and acceptance criteria, which a herbal drug/preparation should conform to be considered acceptable for its intended use:
Definition, Characters, Identification, Tests, Assay (wherever possible)



Assay

- **if the constituents with known therapeutic activity or active markers are known (in case of quantified or standardised extracts) these are used for assay**
- **specific assays (single substance/ group of substances) are preferred, but also group determinations (e.g. titration) are used**
- Liquorice, ethanol liquid extract, standardised (3.0 – 5.0 % glycyrrhizic acid / HPLC)
- Fresh Bilberry fruit dry extract, refined and standardised (32.4 – 39.6 % anthocyanins / HPLC sum of different anthocyanins expressed as cyanidin-3-O-glucoside chloride)
- Ginkgo dry extract, refined and quantified (22.0 – 27.0 % flavonoids/ HPLC; 2.6 – 3.2 % bilobalide; 2.8 – 3.4 % ginkgolides A, B, C / HPLC; maximum 5 ppm ginkgolic acids)
- Hawthorn leaf and flower liquid extract, quantified (0.8 – 3.0 % flavonoids / spectrophotometry)
- Belladonna leaf dry extract (0.95 – 1.05% alkaloids / titration)



Assay (herbal drugs/preparations)

- **in any other cases analytical markers are used**
- Devils claw dry extract (not less than 1.5% harpagoside / HPLC)
- Buckwheat herb (not less than 4.0% rutin / HPLC)
- Passion flower (not less than 1.5 flavonoids / spectrophotometry)
- Hamamelis leaf (not less than 3 % tannins / 2.8.14 spectrophotometry)
- Ginger root (not less than 15 ml/kg essential oil / 2.8.12)



Assay Specific marker vs group assay

- **Specific assay / marker(s)**
 - advantage
 - specific
 - can be used in control of the manufacturing process of finished product
 - can be used in stability testing
 - disadvantage
 - research effort to find marker
 - needs reference substance
 - method development may be difficult
 - may be present in low amount
 - may be unstable
- **Group assay**
 - advantage
 - easy to perform
 - reference is available
 - can be used in control of the manufacturing process of finished product
 - can be used in stability testing
 - represents a significant amount of the extract
 - disadvantage
 - specificity is limited



Group determinations / Ph. Eur.

- Tannins, 2.8.14
- Essential oil, 2.8.12
- Flavonoids (important group of secondary plant metabolites)
 - spectrophotometry (AlCl₃, boric acid- oxalic acid)
 - HPLC, e.g. Ginkgo leaf (after hydrolysis), Buckwheat herb, St. John`s wort dry extract
- advantages / HPLC
- more specific than spectrophotometry
- HPLC (after hydrolysis): universal use, high sample throughput possible
- can be used in stability studies



Group determinations / flavonoids / HPLC

- specificity



Determination of flavonoids in homeopathic mother tinctures using HPLC (according monograph Ginkgo leaf) *

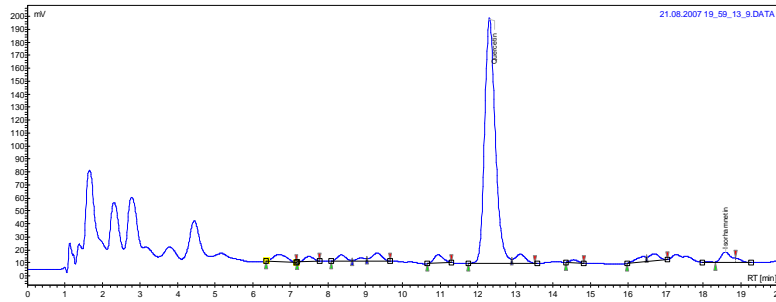
Mother tincture	Flavonols (%)**			sum
	quercetin	kaempferol	isorhamnetin	
Allium	0.0156	0	0	0.0156
Ceanothus americanus	0.1731	0.0076	0	0.1807
Clematis	0.0209	0.0094	0	0.0303
Drosera	0.1125	0.0035	0	0.1160
Eupatorium perfoliatum	0.0277	0.0126	0	0.0403
Galega officinalis	0.0154	0.0175	0.0030	0.0359
Ginkgo biloba	0.0348	0.0288	0.0050	0.0686
Happlopappus	0.0360	0.0194	0.0114	0.0668
Iberis amara	0.0107	0.0082	0.0030	0.0219
Ononis spinosa	0.0075	0.0316	0	0.0391
Populus tremula	0.0207	0.0068	0	0.0275
Sambucus nigra	0.0223	0.0030	0.0067	0.0320
Solidago virgaurea	0.0147	0.0095	0	0.0242

* according Annex I of Directive 2001/83 an assay in homeopathic mother tinctures is only required if toxic compounds are present

** quantitation limit 0.0030%



Mother tincture *Allium cepa* (prepared according HAB)
Fresh bulbs of *Allium cepa* L.

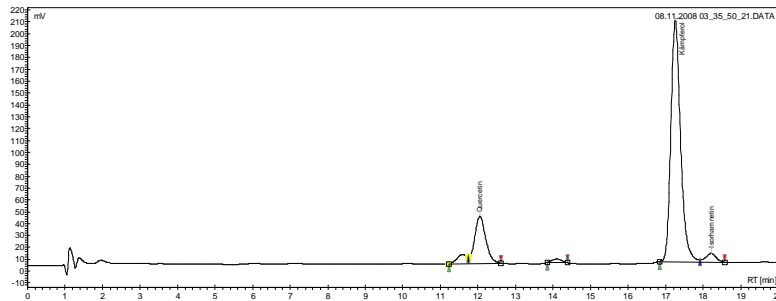


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Mother tincture *Ononis spinosa* (prepared according method 3a HAB)
Fresh aerial parts of *Ononis spinosa* L., collected at flowering time

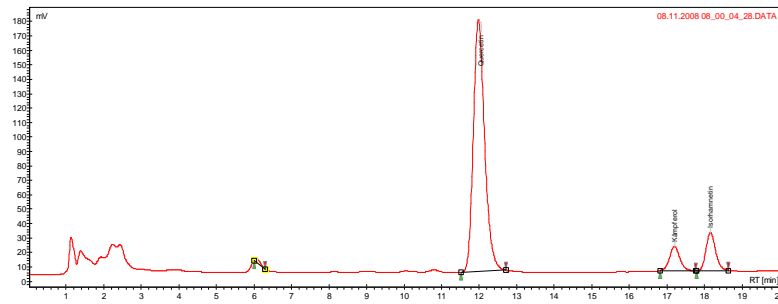


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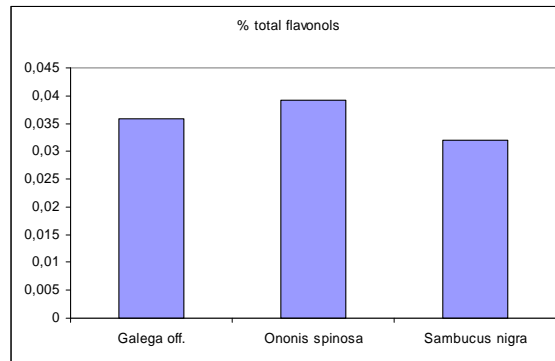
**Mother tincture *Sambucus nigra* (prepared according method 3a HAB)
Equal parts of fresh leaves and inflorescences of *Sambucus nigra* L.**



Group determinations / flavonoids / HPLC

- specificity / ratio

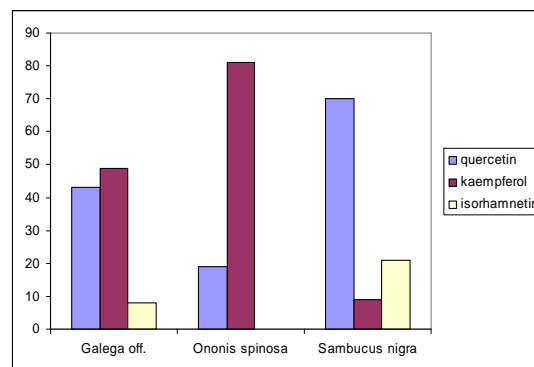
Determination of flavonoids in homeopathic mother tinctures using HPLC
(according monograph Ginkgo leaf)



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Determination of flavonoids in homeopathic mother tinctures using HPLC
(according monograph Ginkgo leaf)
Ratio quercetin : kaempferol : isorhamnetin



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Group determinations / flavonoids / HPLC

- batch to batch control



Determination of flavonoids in different batches Aconitum mother tinctures using HPLC

batch	quercetin	Flavonols (%)	
		kaempferol	isorhamnetin
1	0.0175	0.0091	0
2	0.0276	0.0125	0
3	0.0147	0.0142	0
4	0.0182	0.0133	0
mean	0.0195	0.0123	
SD	0.0056	0.0022	
CV	28.8	18.1	

Determination of flavonoids in different batches Aconitum mother tinctures using HPLC Ratio



batch	Ratio		
	quercetin :	kaempferol :	isorhamnetin
1	66	34	0
2	69	31	0
3	51	49	0
4	58	42	0
mean	60.8	39.2	
SD	8.1	8.1	
CV	13.3	20.7	

Conclusion



- specific markers are first choice to characterise a herbal drug/preparation.
- group determinations as already used in the Ph. Eur. are helpful options, especially for the elaboration of new monographs (not well characterised plants, no specific marker known or low concentrated marker)
- the determination of flavonoids as described in different monographs of the Ph. Eur. may be completed by the HPLC method as described in the monograph Ginkgo leaf. The description of the method as a general text should be considered



Thank you for your attention

Deutsche Homöopathie-Union, Karlsruhe

INTERNATIONAL SYMPOSIUM ON
HERBAL DRUGS AND HERBAL DRUG PREPARATIONS
25 SEPTEMBER 2009
VIENNA

Up-date on methods and limits for the Microbiological Quality of Herbal Medicinal Products

Dr Keith Helliwell
William Ransom & Son plc



1

Background

European Pharmacopoeia **6.0** (effective from date: 1st January 2008)

Chapter 5.1.4: Microbiological Quality of Pharmaceutical Preparations.

Method A (*Pre harmonised method*) effective **to** date: 31st December 2008.

Method B (*Harmonised method*) effective **from** date: 1st January 2009.

European Pharmacopoeia Supplement 6.3 (effective from date: 1st January 2009).

Chapter 5.1.4: Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use. (*Harmonised method only*).

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Working Party MQH

- Development of Texts
- Chapter 2.6.31: Microbiological Examination of Herbal Medicinal Products for Oral Use.
- Chapter 5.1.8.
Microbiological Quality of Herbal Medicinal Products for Oral Use

3

Background

5.1.4: Microbiological Quality of Pharmaceutical Preparations

The following chapter is published for information. This general chapter present 2 sets of recommended acceptance criteria for microbiological quality. The 1st set of criteria corresponds to the 1st sets of methods in general chapters 2.6.12 and 2.6.13. In the same way that the 1st sets of tests in chapters 2.6.12 and 2.6.13 are to be replaced in future by the 2nd sets, so that 1st set of criteria in this chapter will be replaced by the 2nd set. Where authorised, the 2nd set of criteria may be used instead of the 1st set before replacement of the latter. The second set presents criteria developed in co-operation with the Japanese Pharmacopoeia and the United States Pharmacopoeia to achieve harmonised requirements.

A: METHOD OF THE EUROPEAN PHARMACOPOEIA

In the manufacture, packaging, storage and distribution of pharmaceutical preparations, suitable measures must be taken to ensure their microbiological quality. The pharmaceutical preparations should comply with the criteria given below.

Category 3:

B: Preparations for oral administration containing raw materials of natural (animal, vegetable or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts microbial contamination of the raw material exceeding 10³ viable micro-organisms per gram or per millilitre. Herbal medicinal products described in Category 4 are excluded.

- Total viable aerobic count (2.6.12). Not more than 10⁴ bacteria and not more than 10² fungi per gram or per millilitre.
- Not more than 10² enterobacteria and certain other gram-negative bacteria per gram or per millilitre (2.6.13).
- Absence of *Salmonella* (10g or 10ml) (2.6.13).
- Absence of *Escherichia coli* (1g or 1ml) (2.6.13).
- Absence of *Staphylococcus aureus* (1g or 1ml) (2.6.13).

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Background

5.1.4: Microbiological Quality of Pharmaceutical Preparations

Category 4:

A: Herbal medicinal products to which boiling water is added before use.

- Total viable aerobic count (2.6.12). Not more than 10^7 bacteria and not more than 10^5 fungi per gram or per millilitre.
- Not more than 10^2 enterobacteria and certain other gram-negative bacteria per gram or per millilitre (2.6.13).

B: Herbal medicinal products to which boiling water is not added before use.

- Total viable aerobic count (2.6.12). Not more than 10^5 bacteria and not more than 10^4 fungi per gram or per millilitre.
- Not more than 10^3 enterobacteria and certain other gram-negative bacteria per gram or per millilitre (2.6.13).
- Absence of *Escherichia coli* (1g or 1ml) (2.6.13).
- Absence of *Salmonella* (10g or 10ml) (2.6.13).

Chapter 2.6.12: Microbiological Examination of Non-sterile products; total viable count.

A: Method of the European Pharmacopoeia. Interpretation of results.

When a limit is prescribed in a monograph it is interpreted as follows:

10^2 micro-organisms: maximum acceptable limit 5×10^2 .

10^3 micro-organisms: maximum acceptable limit: 5×10^3 ; and so forth.

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Background

5.1.4. MICROBIOLOGICAL QUALITY OF NON-STERILE PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE.

Table 5.1.4.1: Acceptance criteria for microbiological quality of non-sterile dosage forms

Route of Administration	TAMC (CFU/g or CFU/ml)	TYMC (CFU/g or CFU/ml)	Specified micro-organisms
Non-aqueous preparations for oral use	10^3	10^2	Absence of <i>Escherichia coli</i> (1g or 1ml)
Aqueous preparations for oral use	10^2	10^1	Absence of <i>Escherichia coli</i> (1g or 1ml)
Rectal use	10^3	10^2	
Oromucosal use / Gingival use / Cutaneous use / Nasal use / Auricular use	10^2	10^3	Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml)
Vaginal use	10^2	10^1	Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml) Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Candida albicans</i> (1g or 1ml)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml)
Inhalation use (special requirements apply to liquid preparations for nebulisation)	10^2	10^1	Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml) Absence of bile-tolerant gram-negative bacteria (1g or 1ml)
Special Ph. Eur. Provision for oral dosage forms containing raw materials of natural (animal, <u>vegetal</u> or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU per gram or per millilitre	10^4	10^2	Not more than 10^2 CFU of bile-tolerant gram-negative bacteria (1g or 1ml) Absence of <i>Salmonella</i> (10g or 10ml) Absence of <i>Escherichia coli</i> (1g or 1ml) Absence of <i>Staphylococcus aureus</i> (1g or 1ml)
Special Ph. Eur. Provision for herbal medicinal products consisting solely on one or more herbal drugs (whole, reduced or powdered):			
- herbal medicinal products to which boiling water is added before use.	10^7	10^5	Not more than 10^2 CFU of <i>Escherichia coli</i> (1g or 1ml).
- herbal medicinal products to which boiling water is not added before use.	10^5	10^4	Not more than 10^3 CFU of bile-tolerant gram-negative bacteria (1g or 1ml) Absence of <i>Escherichia coli</i> (1g or 1ml) Absence of <i>Salmonella</i> (10g or 10ml)

When an acceptance criterion for microbiological quality is prescribed it is interpreted as follows:

- 10^1 CFU: maximum acceptable count = 20;
- 10^2 CFU: maximum acceptable count = 200;
- 10^3 CFU: maximum acceptable count = 2000, and so forth

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Background

The process of developing the *Harmonised procedure* was the impetus for a number of different concerns related to Categories 3B, 4A and 4B to be brought to the attention of the European Pharmacopoeia Commission.

As a result, in November 2006 the Commission established Working Party MQH (Microbiological Quality of Herbal Drugs) which has as its remit: *addressing the problem of the microbiological quality of Herbal Medicinal Products.*

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WORKING PARTY MQH

Development of texts:

1st Meeting: 7th March 2007: (Chair: Prof H.G. Kristensen)

Key Issues:

- [1] In Chapter 5.1.4 *Microbiological Quality of Pharmaceutical Preparations*, Categories 3B, 4A and 4B were interpreted differently by National Authorities.
- [2] Over the years there had been many calls for a relaxation of some of the acceptance criteria, particularly for Categories 4A and 4B.
- [3] A proposal in the *Harmonised procedure* to change the acceptance criteria for maximum acceptable counts from 5×10^x to 2×10^x .

As a result, a decision was taken by the Working Party to draft a new General Chapter specific to Herbal Medicinal Products and, post this first meeting, the need for a new General Chapter specifying the methodology to be used.

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WORKING PARTY MQH

Development texts

2nd Meeting: 12th December 2007 (Chair: Prof H. G. Kristensen)

The two newly drafted General Chapters 2.6.31 and 5.1.8 were discussed, modified and subsequently published in Pharmedropa 20.3.

3rd Meeting: 17th December 2008 (Chair: Dr K. Helliwell)

National Authority comments assessed, texts modified for presentation to the EP Commission (17th-18th March 2009).

Adoption of texts: 17th April 2009

4th Meeting: (Chair: Dr K. Helliwell)

26th November 2009

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WORKING PARTY MQH

Chapter 2.6.31: Microbiological Examination of Herbal Medicinal Products for Oral Use

This Chapter supports *Chapter 5.1.8* in that the tests for specified micro-organisms are given here with a cross-reference to *Chapters 2.6.12* and *2.6.13* for the methods for TAMC and TYMC and for recommended media.

Specified micro-organisms:

Escherichia coli

- absence
- enumeration (probable number method – semi-quantitative)

Bile-tolerant Gram-negative bacteria

- enumeration (probable number method – semi-quantitative)

Salmonella

- Absence

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WORKING PARTY MQH

FORGET pre-harmonised General Chapter 5.1.4 and

Categories 3B, 4A and 4B



THEY NO LONGER EXIST!

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WORKING PARTY MQH

Chapter 5.1.8 Microbiological Quality of Herbal Medicinal Products for Oral Use

A: Herbal medicinal products containing herbal drugs, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (for, example herbal teas, with or without added flavourings).

TAMC	Acceptance criterion: 10^7 CFU/g Maximum acceptable count: 50 000 000 CFU/g
TYMC	Acceptance criterion: 10^5 CFU/g Maximum acceptable count: 500 000 CFU/g
<i>Escherichia coli</i>	Acceptance criterion: 10^3 CFU/g •
<i>Salmonella</i>	Absence (25g) •

B: Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where the method of processing (for example, extraction) or, where appropriate, in the case of herbal drugs, or pre-treatment reduces the level of organisms to below those stated for this category

TAMC	Acceptance criterion: 10^4 CFU/g/ or CFU/ml Maximum acceptable count: 50 000 CFU/g or CFU/ml
TYMC	Acceptance criterion: 10^2 CFU/g or CFU/ml Maximum acceptable count: 500 CFU/g or CFU/ml
Bile-tolerant gram-negative bacteria	Acceptance criterion: 10^2 CFU/g or CFU/ml
<i>Escherichia coli</i>	Absence (1g or 1ml)
<i>Salmonella</i>	Absence (25g or 25ml) • •

C: Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where it can be demonstrated that the method of processing (for example, extraction with low strength alcohol or water that is not boiling or low temperature concentration) or, in the case of herbal drugs, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required under B.

TAMC	Acceptance criterion: 10^5 CFU/g/ or CFU/ml Maximum acceptable count: 500 000 CFU/g or CFU/ml
TYMC	Acceptance criterion: 10^4 CFU/g or CFU/ml Maximum acceptable count: 50 000 CFU/g or CFU/ml
Bile-tolerant gram-negative bacteria	Acceptance criterion: 10^4 CFU/g or CFU/ml •
<i>Escherichia coli</i>	Absence (1g or 1ml)
<i>Salmonella</i>	Absence (25g or 25ml) •

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WORKING PARTY MQH

Chapter 5.1.8: Microbiological Quality of Herbal Medicinal Products for Oral Use

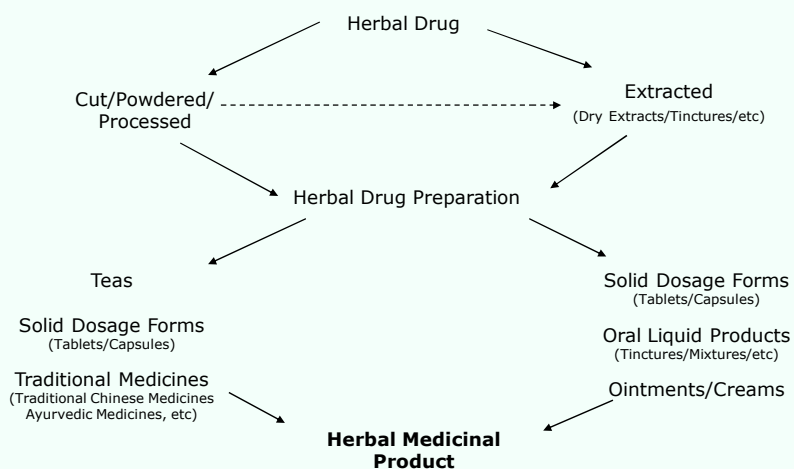
It is recognised that for some medicinal products containing herbal drugs and/or herbal drug preparations the criteria given under A, B or C above for TAMC, TYMC and bile-tolerant gram-negative bacteria cannot be met because of the typical level of microbial contamination. Higher acceptance criteria may be applied on the basis of a risk assessment that takes account of qualitative and quantitative characterisation of the bioburden and the intended use of the medicinal product.

If it has been shown that none of the prescribed tests will allow valid enumeration of micro-organisms at the level prescribed, a validated method with a limit of detection as close as possible to the indicated acceptance criterion is used.

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WORKING PARTY MQH

Chapter 5.1.8 Microbiological Quality of Herbal Medicinal Products for Oral Use



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WORKING PARTY MQH

Chapter 5.1.8. Microbiological Quality of Herbal Medicinal Products for Oral Use

Issues arising from the adoption of Chapter 5.1.8.

- Requirement to define **Herbal Medicinal Product** in the General Notices.
- General monograph on **Extracts** makes reference to *Chapter 5.1.4*.
- General monograph on **Herbal Drugs** makes reference to *Chapter 5.1.4*.
- General monograph on **Herbal Teas** makes reference to *Chapter 5.1.4*.
- General monograph on **Herbal Drugs for homeopathic preparations** makes reference to *Chapter 5.1.4*.
- *Chapter 5.1.4, Table 5.1.4-1*

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WORKING PARTY MQH

Chapter 5.1.8: Microbiological Quality of Herbal Medicinal Products for Oral Use

- Requirement to define **Herbal Medicinal Product** in the General Notices.

The following has been introduced into the **General Notices** under:

1.1 GENERAL STATEMENTS

Conventional terms

Herbal medicinal product. Any medicinal product exclusively containing as active ingredients one or more herbal drugs or one or more herbal drug preparations, or one or more such herbal drugs in combination with one or more such herbal drug preparations.

[Adopted by European Pharmacopoeia Commission on 17th April 2009]

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WORKING PARTY MQH

Chapter 5.1.8: Microbiological Quality of Herbal Medicinal Products for Oral Use

- General monograph on **Herbal Teas** makes reference to *Chapter 5.1.4*. The following editorial alteration will be made to the general monograph: **Herbal Teas**.

DEFINITION

Recommendations on the microbiological quality of herbal teas (5.1.8 *Microbiological Quality of Herbal Medicinal Products for Oral Use*) takes into account the prescribed preparation method (use of boiling or non-boiling water).

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WORKING PARTY MQH

Chapter 5.1.8: Microbiological Quality of Herbal Medicinal Products for Oral Use

- General monograph on **Extracts** makes reference to *Chapter 5.1.4* under TESTS as follows: where applicable, as a result of analysis of the herbal drug or animal matter used for production and in view of the production process, tests for microbiological quality (5.1.4), heavy metals.....in the extracts may be necessary.

In addition, there are 3 monographs on extracts

- Belladonna Leaf Dry Extract, Standardised
- Frangula Bark Dry Extract, Standardised
- Senna Leaf Dry Extract, Standardised

which contain the following specific requirements under TESTS:

Microbial contamination

TAMC: acceptance criterion 10^4 CFU/g (2.6.12)

TYMC: acceptance criterion 10^2 CFU/g (2.6.12)

Absence of *Escherichia coli* (2.6.12)

Absence of *Salmonella* (2.6.13)

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WORKING PARTY MQH

Chapter 5.1.8: Microbiological Quality of Herbal Medicinal Products for Oral Use

- General monograph on **Herbal Drugs** makes reference to *Chapter 5.1.4* under TESTS as follows:

Microbial contamination: Recommendations on the microbiological quality of herbal medicinal products consisting solely of one or more herbal drugs are given in the text *5.1.4: Microbiological quality of pharmaceutical preparations (sic)*.

Where necessary, herbal drugs comply with other tests, such as the following, for example:

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WORKING PARTY MQH

Chapter 5.1.8: Microbiological Quality of Herbal Medicinal Products for Oral Use

- General monograph on **Herbal Drugs for homeopathic preparations** makes reference *Chapter 5.1.4* under PRODUCTION as follows:

Adequate measures have to be taken in order to ensure that the microbiological quality of homeopathic preparations containing 1 or more herbal drugs comply with the recommendations given in the text on *5.1.4: Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use*.

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WORKING PARTY MQH

Chapter 5.1.4: Microbiological Quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use.

Table 5.1.4.1: Acceptance criteria for microbiological quality of non-sterile dosage forms

Route of Administration	TAMC (CFU/g or CFU/ml)	TYMC (CFU/g or CFU/ml)	Specified micro-organisms
Non-aqueous preparations for oral use	10 ³	10 ²	Absence of <i>Escherichia coli</i> (1g or 1ml)
Aqueous preparations for oral use	10 ²	10 ¹	Absence of <i>Escherichia coli</i> (1g or 1ml)
Rectal use	10 ³	10 ²	
Oromucosal use / Gingival use / Cutaneous use / Nasal use / Auricular use	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml)
Vaginal use	10 ²	10 ¹	Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml) Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Candida albicans</i> (1g or 1ml)
Transdermal patches (limits for one patch including adhesive layer and backing)	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml)
Inhalation use (special requirements apply to liquid preparations for nebulisation)	10 ²	10 ¹	Absence of <i>Staphylococcus aureus</i> (1g or 1ml) Absence of <i>Pseudomonas aeruginosa</i> (1g or 1ml) Absence of bile-tolerant gram-negative bacteria (1g or 1ml)
Special Ph. Eur. Provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10 ³ CFU per gram or per millilitre	10 ⁴	10 ²	Not more than 10 ² CFU of bile-tolerant gram-negative bacteria (1g or 1ml) Absence of <i>Salmonella</i> (10g or 10ml) Absence of <i>Escherichia coli</i> (1g or 1ml) Absence of <i>Staphylococcus aureus</i> (1g or 1ml)

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WORKING PARTY MQH

Dr. V. Acquati (Italy) Dr. E. Charton (EP Secretariat)
 Mr. Y. Cortez (France) Ms. C. Gustafsson (EP Secretariat)
 Dr. R. Hubinette (Sweden)
 Dr. B. Klier (Germany)
 Prof. R. Laenger (Austria)
 Dr S. Y. Wang-Tschen (Switzerland)

Thank you to each of the current members of WP MQH.

Thank you for your kind attention.

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William Ransom & Son plc
51-53 Mead Industrial Estate
Burymead Road
Hitchin
Herts
SG5 1RT
ENGLAND

Tel: 00 44 (0) 1462 477035

Fax: 00 44 (0) 1462 477089

E-mail: khelliwell@williamransom.com

Web: www.williamransom.com

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Development of the HMPC's work program

Burt Kroes

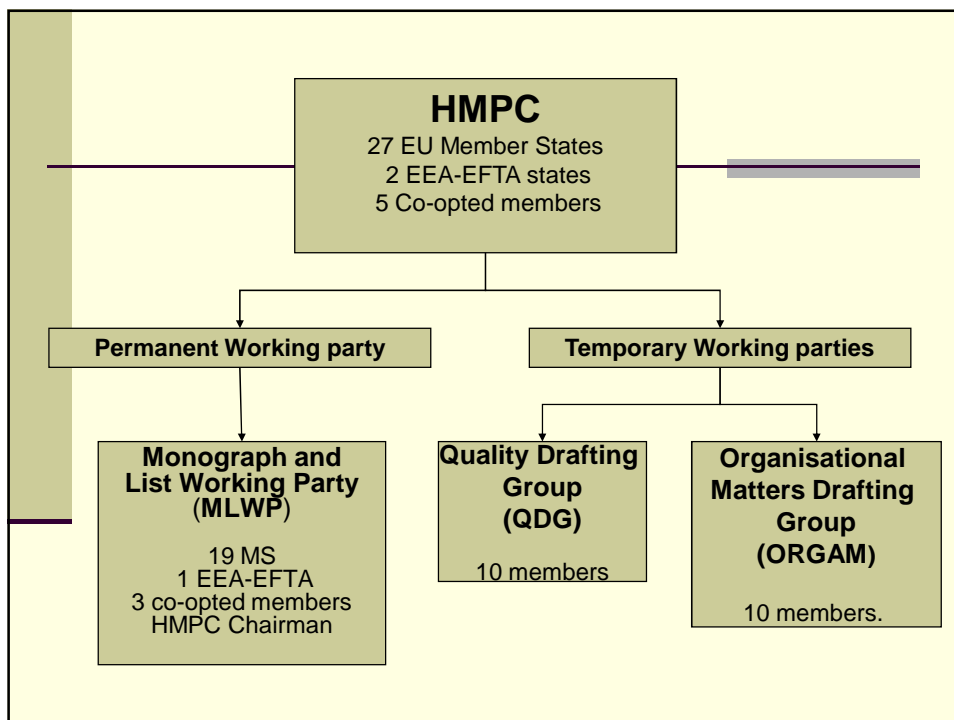
Content

- General information on HMPC
- Work program
- (Future) Collaboration with EDQM

Herbal medicinal Products Committee (HMPC)

“The HMPC's activities aim at *assisting the harmonisation of procedures* and provisions concerning herbal medicinal products laid down in EU Member States, and further integrating herbal medicinal products in the European regulatory framework. As part of these objectives, the HMPC *provides* EU Member States and European institutions its *scientific opinion on questions relating to herbal medicinal products*. Other core tasks include *the establishment of a draft 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products'*, as well as *the establishment of Community herbal monographs...*”

<http://www.emea.europa.eu/htms/general/contacts/HMPC/HMPC.html>



The screenshot shows the EMA website with a red box highlighting the following navigation links:

- Community List
- Community Monographs
- Calls for submission of scientific data
- Regulatory and procedural guidance
- Guidance Documents
- Information for patients

The larger red box contains the following text:

Community List

Community Monographs

Calls for submission of scientific data

Regulatory and procedural guidance

Guidance Documents

Information for patients

ENTRY TO LIST OF HERBAL SUBSTANCES, PREPARATIONS AND COMBINATIONS THEREOF FOR USE IN TRADITIONAL HERBAL MEDICINAL PRODUCTS:	
<i>CALENDULA OFFICINALIS</i> L., FLOS	
Scientific name of the plant	
<i>Calendula officinalis</i> L., flos	
Botanical family	
Asteraceae	
Herbal substance	
Calendula flower	
Common name in all EU official languages of herbal substance	
BG (bългарски):	IT (italiano):
CS (čeština): měsíčkový květ	LT (lietuvių kalba):
DA (dansk):	LV (latviešu valoda):
DE (Deutsch): Ringelblumenblüten	MT (malti):
EL (ελληνικά):	NL (nederlands): Goudbloem
EN (English): calendula flower	PL (polski): kwiat nagietka
ES (español): Calendula, flor de	PT (português):
ET (eesti keel): saialilleõisik	RO (română):
FI (suomi): kehäkukka	SK (slovenčina): Nechtíkový kvet
FR (français): Souci	SL (slovenščina): cvet vrtnega ognjica
HU (magyar):	SV (svenska):
	IS (islandska): morgunfrú, blóm
	NO (norsk):
Herbal preparation(s)	
A) Liquid extract (DER 1:1, ethanol 40-50% v/v)	
B) Tincture (DER 1:5, ethanol 70-90% v/v)	
C) Liquid extract (DER 1:10, fatty vegetable oil, e.g. olive oil)	
D) Ointment (DER 1:5 – 1:25, hardened vegetable fat, petroleum jelly ¹)	
E) Commuted herbal substance for infusion	
European Pharmacopoeia monograph reference	
Calendula flower - Calendulae flos 01/2005:1297	

Community List entries (9)

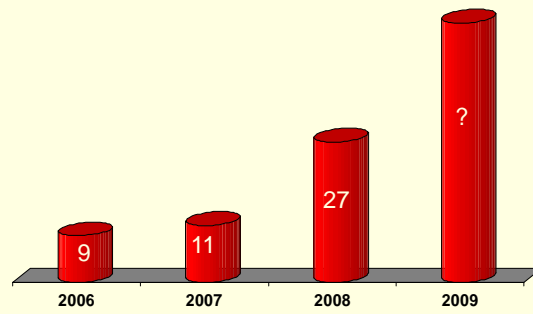
1. Menthae piperitae aetheroleum *Mentha x piperita* L. (peppermint oil)
2. Anisi fructus *Pimpinella anisum* L. (aniseed)
3. Calendulae flos *Calendula officinalis* L. (calendula flower)
4. Eleutherococci radix *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (eleutherococcus root)
5. Echinaceae purpureae herba *Echinacea purpurea* (L.) Moench (purple coneflower herb)
6. Foeniculi dulcis fructus *Foeniculum vulgare* Miller subsp. *vulgare* var. *dulce* (Miller) Thellung. (sweet-fennel fruit)
7. Foeniculi amari fructus *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare* (bitter-fennel fruit)
8. Linum semen *Linum usitatissimum* L. (linseed)
9. Valerianae radix *Valeriana officinalis* L. (valerian root)



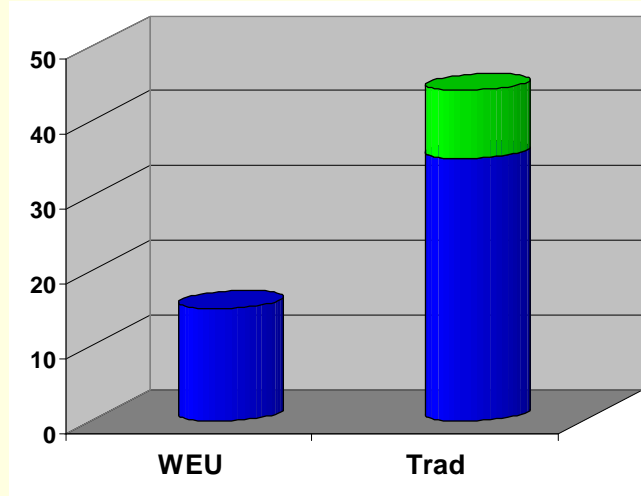
The image shows a screenshot of the European Medicines Agency (EMA) website. A navigation menu is visible on the left side, with a red box highlighting the 'Community List' section. The menu items are: Introduction, Community List, Community Monographs, Calls for submission of scientific data, Regulatory and procedural guidance, Guidance Documents, and Information for patients. The 'Community List' section is further detailed with a list of items: HMPPC, Role, composition & rules of procedure, Meetings, Meeting Reports, Inaugural Meeting, Working parties & other groups, Status Report - Oct 2006, Interested Parties to the HMPPC, HMPWP Documents (1997-2004), Press Releases, and Working Documents. A large red-bordered box on the right side of the screenshot contains the following text:

- Community List**
- Community Monographs**
- Calls for submission of scientific data**
- Regulatory and procedural guidance**
- Guidance Documents**
- Information for patients**

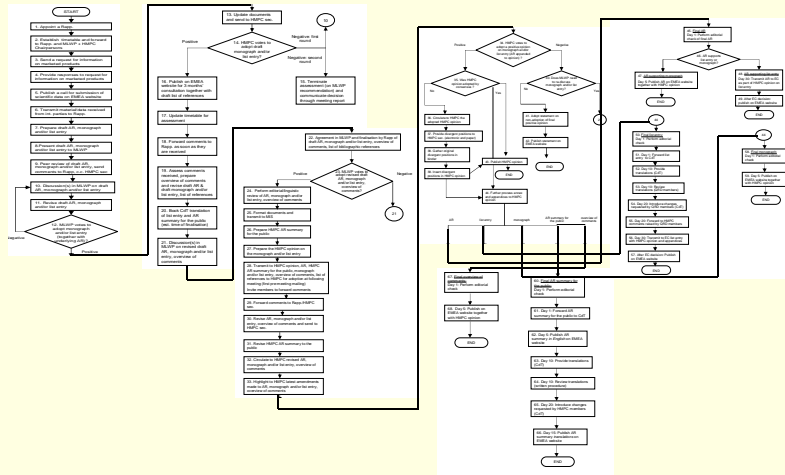
Monographs



Monographs finalized (56)



Flow chart of the processes related to establishment and publication of Community herbal monographs and entries to the Community list of herbal substances



Human Medicines - Herbal Medicinal Products

Committee on Herbal Medicinal Products (HMPC) - Community Monographs

Salicis cortex

Salicis cortex *Salix purpurea* L.; *Salix daphnoides* Vill.; *Salix fragilis* L., cortex

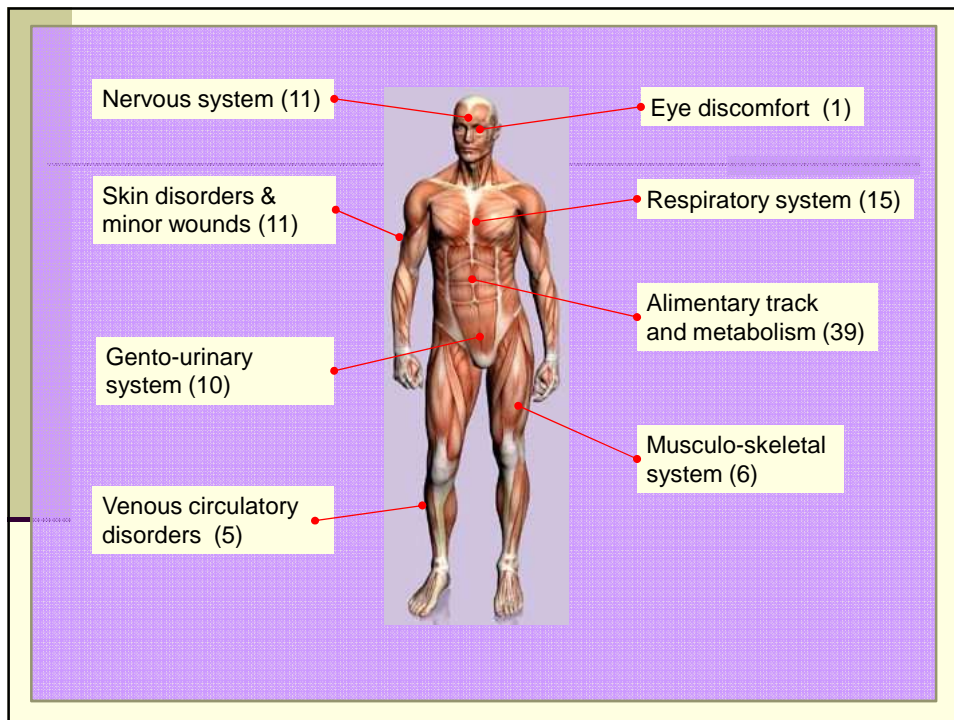
Published 13/02/09

Draft	BG	ES	CS	DA	DE	ET	EN	FR	IT	LV	LT	HU	MT	NL	PL	PT	RO	SK	SL	FI	SV	
EN																						

- See Glossary of language codes...
1. HMPC opinion on a Community herbal monograph
 2. Summary of assessment report
 3. Community herbal monograph
 4. HMPC assessment report
 5. List of references for assessment report
 6. Overview of comments received on HMPC monograph

Glossary

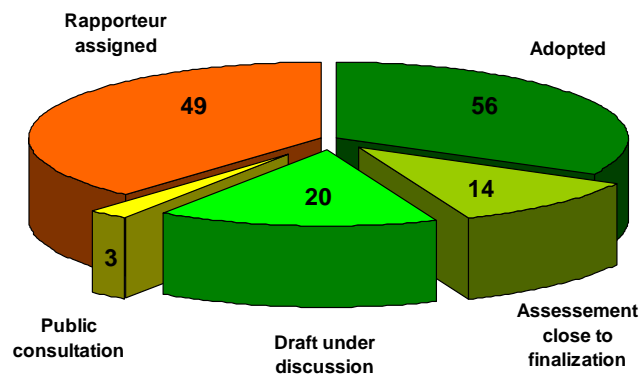
BG	=	bългарски
ES	=	español
CS	=	čeština
DA	=	dansk
DE	=	Deutsch
ET	=	eesti keel
EL	=	ελληνικά
EN	=	English
FR	=	français
IT	=	italiano
LV	=	latviešu valoda
LT	=	lietuvių kalba
HU	=	magyar
MT	=	Malti
NL	=	Nederlands
PL	=	polSKI
PT	=	português
RO	=	română
SK	=	slovenčina
SL	=	slovenščina
FI	=	suomi
SV	=	svenska



Well Established Use

- *Aloe barbadensis* Miller; Aloe (mainly *Aloe ferox* Miller and its hybrids) (barbados aloes; cape aloes)
- *Echinacea purpurea* (L.) Moench (purple coneflower herb)
- *Rhamnus frangula* L. (frangula bark)
- *Aesculus hippocastanum* L., semen (horse chestnut seed)
- *Linum semen* *Linum usitatissimum* L. (linseed)
- *Menthae piperitae* folium *Mentha x piperita* L. (peppermint leaf)
- *Plantaginis ovatae* semen *Plantago ovata* Forssk. (ispaghula seed)
- *Plantaginis ovatae* seminis tegumentum *Plantago ovata* Forssk. (ispaghula husk)
- *Psyllii semen* *Plantago afra* L.; *Plantago indica* L. (*psyllium* seed)
- *Rhamni purshianae cortex* *Rhamnus purshianus* D.C. (cascara)
- *Rhei radix* *Rheum palmatum* L.; *Rheum officinale* Baillon (rhubarb)
- *Salicis cortex* *Salix purpurea* L.; *Salix daphnoides* Vill.; *Salix fragilis* L., cortex
- *Sennae folium* *Cassia senna* L.; *Cassia angustifolia* Vahl (senna leaf)
- *Sennae fructus* *Cassia senna* L.; *Cassia angustifolia* Vahl (senna pods)
- *Valerianae radix* *Valeriana officinalis* L. (Valerian root)

Work program MLWP Monographs and List entries



Community List

Community Monographs

Calls for submission of scientific data

Regulatory and procedural guidance

Guidance Documents

Information for patients

Guidance documents

- **General (7)**
- **Community List and Monographs (22)**
 - Inventory of herbal substances for assessment Updated *August 26, 2009*
 - Overview of HMPC assessment work - priority list
 - Establishment of Community herbal monographs and Community list entries and related documents



European Medicines Agency
Evaluation of Medicines for Human Use

London, 12 August 2009
Doc. Ref.: EMEA/HMPC/278067/2006

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

Overview of HMPC assessment work – status July 2009

Priority list

Listed in alphabetical order

R: Rapporteur assigned, **C:** ongoing call for scientific data, **D:** Draft under discussion, **P:** Draft published, **PF:** Assessment close to finalisation (pre-final), **F:** Final opinion adopted

Absinthii herba (F)	Curcumae longae rhizoma (PF)	Juniperi pseudo-fructus (PF)
Achilleae millefolii flos (R)	Curcumae xanthorrhizae rhizoma (R)	Lavandulae aetheroleum (R)
Agni casti fructus (D)	Cynarae folium (R)	Lavandulae flos (R)
Agrimoniae herba (R)	Echinaceae angustifoliae radix (D)	Levistici radix (R)
Agropyri repentis rhizoma (R)	Echinaceae pallidae radix (F)	Lichen islandicus (R)
Allii sativi bulbos (R)	Echinaceae purpureae herba (F)	Lini semen (F)
Aloe (F)	Echinaceae purpureae radix (P)	Liquiritiae radix (R)
Althaeae radix (F)	Eleutherococci radix (F)	Lupuli flos (F)
Anisi aetheroleum (F)	Euaseti herba (F)	Manubii herba (C)
Anisi fructus (F)		Mate folium (P)

The image shows a screenshot of the European Medicines Agency (EMA) website. A red box highlights the 'Community List' section in the left-hand navigation menu. Another red box highlights a list of key website sections: 'Community List', 'Community Monographs', 'Calls for submission of scientific data', 'Regulatory and procedural guidance', 'Guidance Documents', and 'Information for patients'. A third red box highlights the text 'Regulatory and procedural guidance' in the main content area of the page.

Regulatory and procedural guidance

- **Quality (21)**
- **Safety (12)**
- **Efficacy (5)**
- **Organisational matters (2)**
- **Pharmacovigilance (13)**
- **Questions & Answers (1)**

Recent guidance documents published by the HMPC QDG

- **Reflection paper on stability** testing of herbal medicinal products and traditional herbal medicinal products
- List of **questions & answers** (Q&A) received during the HMPC assessors training on quality issues emerging for herbal medicinal products (held on 7 December 2007, EMEA)
- **Reflection paper on level of purification** of extracts to be considered as herbal preparations
- Draft **Guideline on selection of test materials for genotoxicity** testing for traditional herbal medicinal products/herbal medicinal products
- **Markers** used for quantitative and qualitative analysis of Herbal Medicinal Products and traditional Herbal Medicinal Products
- **Declaration** of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products in the SPC
- **Quality of Combination** Herbal Medicinal Products / Traditional Herbal Medicinal Products

Community List

Community Monographs

Calls for submission of scientific data

Regulatory and procedural guidance

Guidance Documents

Information for patients

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FOENICULUM VULGARE MILLER SUBSP. *VULGARE*
VAR. *DULCE* (MILLER) THELLUNG, FRUCTUS

FENNEL FRUIT, SWEET

HMPC assessment report summary for the public

This document is a summary of the assessment report adopted by the Committee on Herbal Medicinal Products (HMPC) that describes the data available on the medicinal use of a herbal substance and the conclusions after evaluating these data.

If you want more information on the HMPC conclusions, read the Community list entry on this herbal medicine. Community list entries are authorised by the European Commission further to the scientific opinion of the HMPC and describe the herbal medicines, including their content, how they are used, what they are used for, how they work and how they can be used safely.

Monographs



- Quality specifications
- Authorized /registered products (not only EU)



- Clinical data
- Pre-clinical data
- Registered/ Authorized products
- Medical use (traditional) use in the EU

Valerian root monographs



Valerian dry hydro-alcoholic extract

“ The extract is produced from the drug using ethanol (45 to 80 per cent V/V) or **methanol** (40 to 55 per cent V/V) by an appropriate procedure.”

Content: minimum 0.25 per cent *m/m* of sesquiterpenic acids, expressed as valerenic acid



WEU

- Herbal preparations
- Extracts prepared with ethanol/water (ethanol 40 -70 % (V/V))

Traditional

- dry extracts prepared with water
- valerian tincture
- expressed juice from fresh root
- valerian root oil

“no single or main active ingredient has been identified”

Peppermint leaf monographs



- Peppermint leaf dry extract **ethanol (30-50 per cent V/V) or water** of minimum 60 °C

- **Content:** minimum 0.5 per cent of rosmarinic acid



- Comminuted herbal substance for tea preparation
- Tincture (1:5; **ethanol 45 % (v/v)**)
- Tincture (1:5; **ethanol 70 % (v/v)**)
- *“ The main active component is the essential oil” .*

Willow bark



Bark

- Content: minimum 1.5 per cent of total salicylic derivatives, expressed as salicin (dried drug).

Dry extract

- Content: minimum 5.0 per cent of total salicylic derivatives, expressed as salicin (dried extract).
- Water or a hydroalcoholic solvent equivalent in strength to a maximum of 80 per cent V/V ethanol.

WEU

- Dry extract (8-14:1) extraction solvent ethanol 70% V/V, 15% total salicin

Traditional

- Dry aqueous extracts (16-20:1; 8-16:1, 16:23-1)
- Liquid extract (1:1), extraction solvent ethanol 25% V/V
- Tincture (1:5), extraction solvent ethanol 25% v/v

Coordination HMPC/EDQM



- HMPC observers in Expert groups
- Certification Steering Committee

- EDQM observer in HMPC and QDG
- (Annual?) meeting the the chairs group 13a/b/c

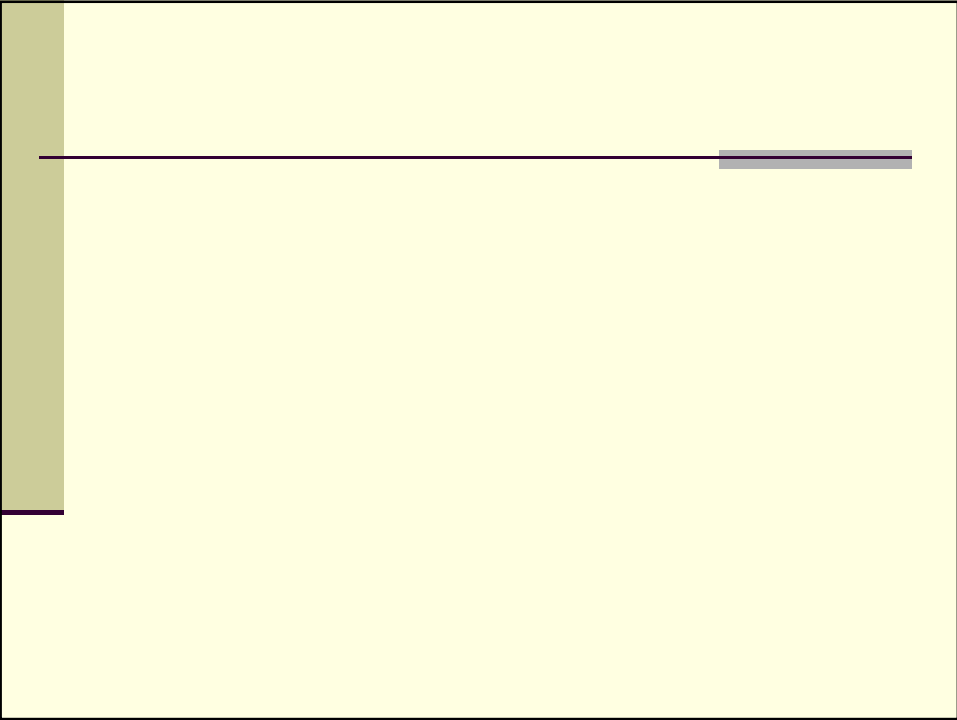
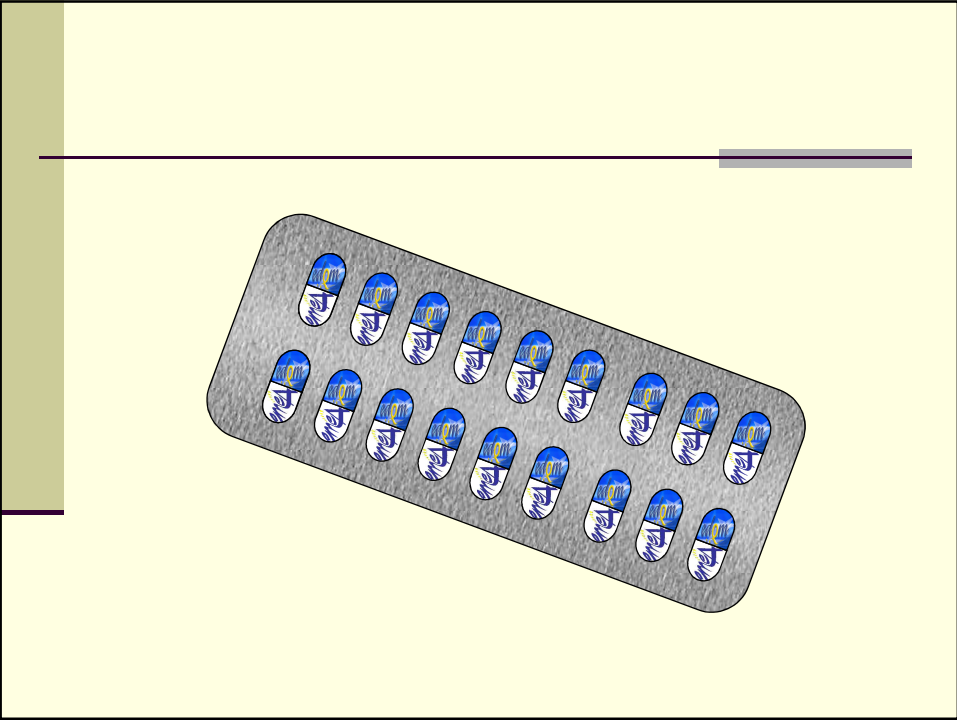
Coordination QDG/EDQM

Issues discussed during the meeting between QDG and the chairs of groups 13A and 13B and TCM

- Role and classification of markers
- Classification of extracts
- Which level of purification is still considered an extract or a herbal preparation?
- Heavy metals and Microbiological limits for herbal drugs
- Implementation of new assay methods

Coordination HMPC/EDQM Topics

- Harmonization of terminology for herbal drugs/substances and preparations
- Coordination of monograph (update)
- Markers; role, selections, classification



UPDATE ON EDQM'S WORK PROGRAMME

Including a progress report on
Traditional Chinese Medicines
(TCM)



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1

General overview

- Monographs in the Ph. Eur: ~ 2100
- Herbal drugs and Herbal drug preparations: 215
 - Herbal drugs: 141
 - Herbal drug preparations: 74



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2

General overview

- Herbal drug preparations
 - Extracts: 43
 - Standardised extracts: 15 (including 4 tinctures)
 - Quantified extracts: 4
 - Other extracts: 24 (including 11 tinctures)
 - Essential oils: 31



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3

General overview

- General monographs:
 - Herbal drugs
 - Herbal drug preparations
 - Herbal teas
 - Extracts
 - Essential oils



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4

General overview

- Methods in Pharmacognosy (2.8)
 - 21 methods are published
- General chapters
 - Microbiological examination of medicinal products containing herbal drugs (2.6.31) (Ph. Eur. 6.7)
 - Microbiological quality of medicinal products containing herbal drugs (5.1.8) (Ph. Eur. 6.7)

General overview

From the 7th edition on the monographs on Herbal drugs and Herbal drug preparations will be published together in the first volume of the Ph. Eur.



easy identification
better handling

Herbal drugs and Herbal drug preparations

- The general monographs on Herbal drugs and Herbal drug preparations have recently been revised.

Publication in: Ph. Eur. supplement 6.8
(January 2010)



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7

Herbal drugs

Introduction of:

- Definitions for whole, fragmented, broken and cut Herbal drugs;
- Maximum limits for certain heavy metals;
- A reference to the general method on ochratoxin A (2.8.22).



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Herbal drugs

Heavy metals. (2.4.27). Unless otherwise stated in an individual monograph or unless otherwise justified and authorised:

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

Where necessary limits for other heavy metals may be required.

Herbal drugs

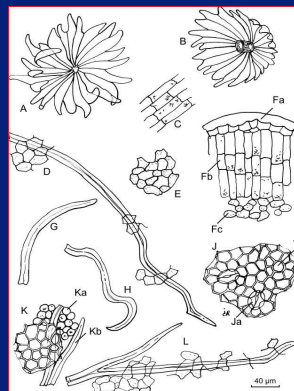
- **Heavy metals:** limits different from the general requirements.
 - Willow bark: cadmium: maximum 2.0 ppm;
 - Tormentil: cadmium: maximum 2.0 ppm;
 - Fumitory: cadmium: maximum 1.5 ppm;
 - Icelandic moss: lead: maximum 10.0 ppm;
 - Kelp (Ph. Eur. 6.0): arsenic: max 90 ppm; cadmium: max 4 ppm; lead: max 5 ppm; mercury: max 0.1 ppm.

Herbal drug preparations

- Changes to the terminology used in the general monograph were made to clarify the scope of the monograph with respect to the monograph on Herbal drugs.
- The reference to instant herbal teas has been removed.

Powder illustrations

- Published in Ph. Eur.: 27
- To be published in Ph. Eur. (6.7 and 6.8): 7
- In Pharmeuropa (21.2 and 21.3): 15



Traditional Chinese Medicines (TCM)

- Work programme (83 monographs):
 - 5 monographs are published;
 - Bistort rhizome
 - Notoginseng root
 - Safflower flower
 - Sanguisorba root
 - Schisandra fruit



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Traditional Chinese Medicines (TCM)

- 2 monographs are adopted and will be published in Ph. Eur. 6.7/6.8 Ephedra herb/Fourstamen stephania root;
- 11 monographs have been published in Pharmeuropa;
- The work on about 45 herbal drugs is ongoing;
- A General chapter on TCM is under preparation.



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Thank you for your attention!



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