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# COMPILATION OF GENERAL QUALITY QUESTIONS ADDRESSED BY THE HMPWP

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*The views presented in this document are those of the HMPWP, which has been created as a forum for exchange of experience in the field of herbal medicinal products. This document is released for the purposes of transparency and has no legal force with respect to Directive 2001/83/EC.*

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**Use of excipients in herbal teas**

The working party addressed questions related to the use of excipients in herbal teas (legislation in place, availability of list of authorised excipients, limitations in amount/percentage of excipients in herbal teas).

Recommendation from the HMPWP:
The views of all delegations were requested and it appeared that a common approach on excipients could be defined as follows:

- the function of each excipient in a herbal tea must be justified (taste, appearance,..)
- usually no more than 3 excipients should be used in a herbal tea (more than 3 excipients imply technical obstacles in terms of quality testing) and excipients should not represent more than 30% of the total weight
- more than 3 excipients or more than 30% of the total weight in a herbal tea would not raise concerns from a public health viewpoint provided that the MAH can control the quality of the product and that appropriate justification on the need for more than 3 excipients is given by the MAH.

**Large variations in markers' specifications**

The working party addressed the question of the acceptability of large variations in markers' specifications. Stability guidelines indicate that a ± 10% variation of the initial value is acceptable. Several Member States reported having seen examples of larger variations for some markers in finished products and the working party discussed what recommendations should be made to address this issue.

Recommendation from the HMPWP:
The working party concluded that requirements in terms of markers' specifications should be as follows:

- applicants should justify the choice of a maker and the proposed specifications
- the general rule for acceptable variations is ± 10%
- wider variations could be accepted if justified on a case-by-case basis.

Unstable markers are poor analytical tools and indicate a questionable selection of these markers, in which case a detailed justification of the choice of markers would be required.

**Quality of water (potable water vs purified water) to be used in preparation of extracts/finished products**

The use of purified water is the preparation of the finished product is required by in all Member States. For the preparation of extracts, a majority of Member States recommend the use of purified water, however, in the framework of mutual recognition the use of potable water of constant, strictly controlled quality may be acceptable, if justified by the applicant. Nevertheless, the applicant would have e.g. to guarantee that a variable composition of the potable water with respect to minerals would not influence the composition of the extract and that there are no public health concerns with respect to the contamination of the potable water. It should be recommended that the quality of potable water be controlled at specified intervals, which should be justified by the applicant.

Recommendation from the HMPWP:
The above recommendations have been introduced in the Note for guidance on Quality of Water for Pharmaceutical use (CPMP/QWP/158/01 - CVMP/115/01) released for consultation in Feb. 2001.

**Acceptability of reference to "organic farming" either in the labelling or in the package leaflet of a herbal medicinal product**

The working party addressed the question of labelling practice for herbal medicinal products in the EU Member States with respect to the acceptability of introducing a reference to organic farming when such cultivation method has been used to produce the raw material of the herbal medicinal product. The European Directive 92/27/EEC makes reference to certain particulars which can appear on the labelling provided that the information is 1) useful to health education, 2) compatible with the SPC of the product and 3) of no promotional nature.
The matter was referred to the Pharmaceutical Committee.

Recommendation from the HMPWP:
The working party took note of the position adopted by the Pharmaceutical Committee at their 49th meeting on 22-23 March 2000. The indication of "accreditation logos", like the "Kosher" and "Halal" or the "organic farming" logo was rejected by the Pharmaceutical Committee. The main reasons given for the rejection of the proposal were that these logos could not be considered as "health information" and that the risk of an inflation of additional items on the packaging required a restrictive interpretation of Directive 92/27.

**Individual quantitative composition for all markers in a finished product**

The HMPWP discussed the manufacturing of a herbal drug preparation (= extract) by mixing four different dried herbal drugs and by percolating the mixture with an extraction solvent. The percolate is either filtered or filtered and concentrated, depending on the pharmaceutical form of the finished product. The manufacturer uses plants both from natural sources and from cultivations depending on availability. The amount of herbal drugs used to manufacture the herbal drug preparation is identical for all batches, irrespective of the contents of marker substances. For the manufacturing of the herbal medicinal product, the amount of herbal drug preparation is identical for all batches, irrespective of the content of marker substances.
The HMPWP was invited to comment on the fact that only one marker substance's content is analysed batch specifically, from the herbal drug preparation or the herbal medicinal product.

The CPMP Note for guidance on the quality of herbal medicinal products mentions in section E "Control tests on the finished product" that:

"The control tests on the finished product must be such as to allow the **qualitative and quantitative determination** of the composition of the active substances and a **specification** has to be given which may be done by using **markers** if constituents with known therapeutic activity are unknown. In the case of herbal drugs or herbal drug preparations with constituents of known therapeutic activity, these constituents must also be **specified and quantitatively determined**.
If a herbal medicinal product contains several herbal drugs or preparations of several drugs and if it is not possible to perform a **quantitative determination** of each active substance, the determination may be carried out jointly for several active substances. The need for this procedure must be justified".

The HMPWP reitereated its position that appropriate justification must be provided when, in exceptional cases, deviating from the requirement to have one marker per herbal drug and to determine individual quantitative composition for all markers in the finished product.
Batch to batch variability in marker content is acceptable as long as it remains within the limits range.

**Declaration of extracts in finished herbal medicinal products**

The HMPWP prepared the following guidance for the declaration of extracts in finished herbal medicinal products.

Examples:

1. Standardised Extracts

   Example: dry extract

2. Quantified Extracts

   Example: dry extract

3. Other Extracts

   Example A: dry extract

   Example B: liquid extract

   Example C: tincture

   Example D: dry extract from a mixture

## Example 1: Standardised Extracts (CPMP/QWP/2819/00)

The following characteristics have to be stated:

1. Name and physical state of the extract
2. Quantity of the genuine extract (as range)
3. Quantity of the constituent(s) with known therapeutic activity
4. Drug to extract ratio (DER)
5. Extraction solvent(s)
6. Name of excipient(s) used for the standardisation

***Details from the extract manufacturer e.g. in the extract specification:***

Dry extract from horse chestnut seed
Constituent(s) with known therapeutic activity:
19% triterpene glycosides, calculated as anhydrous ß-aescin
Quantity of the genuine extract (as range):
70 - 95% genuine extract
DER: 5 – 8 : 1
Excipients for adjustment:
30 - 5% Excipients
Extractions solvent: Methanol 80% (V/V)

Declaration of the finished Product

1 capsule contains:
active substance:
140 - 190 mg of dry extract from horse chestnut seed (5 – 8 : 1)
corresponding to 38 mg triterpene glycoside,
calculated as anhydrous ß-aescin

the extract was manufactured with: Methanol 80% (V/V)

[excipient(s) for standardisation]

**or**

1 capsule contains:
active substance:
140 - 190 mg of dry extract from horse chestnut seed (equivalent to 0.7 – 1.52 g horse chestnut seed)
corresponding to 38 mg triterpene glycoside,
calculated as anhydrous ß-aescin

the extract was manufactured with: Methanol 80% (V/V)

[excipient(s) for standardisation]

## Example 2: Quantified Extracts

The following characteristics have to be stated:

1. Name and physical state of the extract
2. Quantity of the genuine extract
3. Drug to extract ratio (DER)
4. Extraction solvent(s)
5. Content of the quantified constituent(s)

***Details from the extract manufacturer e.g. in the extract specification:***

Dry extract from ginkgo leaf
Quantity of the genuine extract:
100% genuine extract
DER: 35 – 67 : 1
Excipients:
0% Excipients
Extractions solvent: Acetone 60% (m/m)
The extract is quantified of
22.0 to 27.0% of flavonoids expressed as flavone glycosides
2.8 to 3.4% of ginkgolides A, B and C
2.6 to 3.2% of bilobalide
not more than 5 ppm ginkgolic acids

Declaration of the finished Product

1 capsule contains:
active substance:
60 mg of dry extract from ginkgo leaf (35 – 67 : 1)
the extract contains
22.0 to 27.0% of flavonoids expressed as flavone glycosides
2.8 to 3.4% of ginkgolides A, B and C
2.6 to 3.2% of bilobalide

the extract was manufactured with: Acetone 60% (m/m)

**or**

1 capsule contains:
active substance:
60 mg of dry extract from ginkgo leaf (equivalent to 2.1 – 4.02 g of ginkgo leaf)
the extract contains
22.0 to 27.0% of flavonoids expressed as flavone glycosides
2.8 to 3.4% of ginkgolides A, B and C
2.6 to 3.2% of bilobalide

the extract was manufactured with: Acetone 60% (m/m)

**or**

1 capsule contains:
active substance:
60 mg of dry extract from ginkgo leaf (35 – 67 : 1)
corresponding to
13.2 to 16.2 mg of flavonoids expressed as flavone glycosides
1.68 to 2.04 mg of ginkgolides A, B and C
1.56 to 1.92 mg of bilobalide

the extract was manufactured with: Acetone 60% (m/m)

**or**

1 capsule contains:
active substance:
60 mg of dry extract from ginkgo leaf (equivalent to 2.1 – 4.02 g of ginkgo leaf)
corresponding to
13.2 to 16.2 mg of flavonoids expressed as flavone glycosides
1.68 to 2.04 mg of ginkgolides A, B and C
1.56 to 1.92 mg of bilobalide

the extract was manufactured with: Acetone 60% (m/m)

## Example 3A: Other Extracts such as dry extract (CPMP/QWP/2819/00)

The following characteristics have to be stated:

1. Name and physical state of the extract
2. Quantity of the genuine extract
3. Drug to extract ratio (DER)
4. Extraction solvent(s)

***Details from the extract manufacturer e.g. in the extract specification:***

Dry extract from valerian root
Quantity of the genuine extract:
80% genuine extract
DER: 3 – 6 : 1
Excipients:
20% Excipients
Extraction solvent: Ethanol 70% (V/V)

Declaration of the finished Product

1 capsule contains:
active substance:
160 mg of dry extract from valerian root (3 – 6 : 1)
the extract was manufactured with: Ethanol 70% (V/V)

**or**

1 capsule contains:
active substance:
160 mg of dry extract from valerian root (equivalent to 480 – 960 mg of valerian root)
the extract was manufactured with: Ethanol 70% (V/V)

## Example 3B: Other Extracts such as liquid extract

The following characteristics have to be stated:

1. Name and physical state of the extract
2. Quantity of the genuine extract (including extraction solvent)
3. Drug to extract ratio (DER)
4. Extraction solvent(s)

***Details from the extract manufacturer e.g. in the extract specification:***

Liquid extract from thyme (German Pharmacopoeia 2003)
Quantity of the genuine extract:
100% genuine extract
DER: 1 : 2 – 2.5
Excipients:
0% Excipients
Extractions solvent: 1 part ammonia solution 10% (m/m)
20 parts of glycerol 85% (m/m)
70 parts of ethanol 90% (V/V)
109 parts of water

Declaration of the finished Product

5 g [≅ ... ml] of oral solution contain:
active substance:
5 g of liquid extract from thyme (1 : 2 – 2.5)

the extract was manufactured with: ammonia solution 10% (m/m) / glycerol 85% (m/m) / ethanol 90% (V/V) / water (1/20/70/109)

**or**

5 g [≅ ... ml] of oral solution contain:
active substance:
5 g of liquid extract from thyme (equivalent to 2 – 2.5 g thyme)

the extract was manufactured with: ammonia solution 10% (m/m) / glycerol 85% (m/m) / ethanol 90% (V/V) / water (1/20/70/109)

## Example 3C: Other Extracts such as tincture

The following characteristics have to be stated:

1. Name and physical state of the extract
2. Quantity of the genuine extract (including extraction solvent)
3. Drug to extraction solvents ratio or Drug to extract ratio (DER)
4. Extraction solvent(s)

***Details from the extract manufacturer e.g. in the extract specification:***

Tincture from valerian root (German Pharmacopoeia 2003)
Quantity of the genuine extract:
100% genuine extract
Drug to extraction solvents ratio: 1 : 5
Excipients:
0% Excipients
Extractions solvent: Ethanol 70% (V/V)

Declaration of the finished Product

5 g [≅ ... ml] of oral solution contain:
active substance:
5 g of tincture from valerian root (1 : 5)
the extract was manufactured with: Ethanol 70% (V/V)

**or**

5 g [≅ ... ml] of oral solution contain:
active substance:
5 g of tincture from valerian root (1 : x - y)
the extract was manufactured with: Ethanol 70% (V/V)

**or**

5 g [≅ ... ml] of oral solution contain:
active substance:
5 g of tincture from valerian root (equivalent to x – y g valerian root)
the extract was manufactured with: Ethanol 70% (V/V)

## Example 3D: Other Extracts such as dry extract from a mixture

(Herbal substances mixed before the extraction process)

The following characteristics have to be stated:

1. Name and physical state of the extract
2. Quantity of the genuine extract
3. Drug to extract ratio (DER)
4. Extraction solvent(s)

***Details from the extract manufacturer e.g. in the extract specification:***

Dry extract from 3 parts valerian root
2 parts hop strobile
2 parts melissa leaf
Quantity of the genuine extract:
80% genuine extract
DER: 4 – 7 : 1
Excipients:
20% Excipients
Extractions solvent: Ethanol 70% (V/V)

Declaration of the finished Product

1 capsule contains:
active substance:
160 mg of dry extract (4 -7: 1)
from valerian root / hop strobile / melissa leaf (3/2/2)
the extract was manufactured with: Ethanol 70% (V/V)

**or**

1 capsule contains:
active substance:
160 mg of dry extract (equivalent to 0.64 – 1.1 g mixture of the drugs)
from valerian root / hop strobile / melissa leaf (3/2/2)
the extract was manufactured with: Ethanol 70% (V/V)