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Aan de vergunninghouders en aan de industrieapothekers

Betreft: Het correct uitdrukken en verantwoorden van de hoeveelheid actieve bestanddelen in kruidengeneesmiddelen.

Geachte Mevrouw,
Geachte Heer,

In het kader van een registratieaanvraag voor kruidengeneesmiddelen, dient in sommige secties van de CTD-structuur (verplicht bij Koninklijk besluit van 4 MAART 2004 tot wijziging van het koninklijk besluit van 3 juli 1969 betreffende de registratie van geneesmiddelen en tot wijziging van het koninklijk besluit van 6 juni 1960 betreffende de fabricage, de distributie in het groot en de terhandstelling van geneesmiddelen) alsook op de AMM, in de SKP, op de verpakking/etiket en in de bijsluiter, informatie opgenomen/verantwoord te worden over de hoeveelheid actieve bestanddelen die aanwezig is in het kruidengeneesmiddel.

Het document in bijlage aan dit rondschrijven (*Method of expressing the quantity of active ingredients in herbal medicinal products as presented in CTD, AMM and SPC/Package Insert/Labelling*) wil een verduidelijking geven over de manier waarop deze gegevens het beste worden voorgesteld en verantwoord.

Ik dank u bij voorbaat voor de aandacht die u hieraan wilt besteden.

Met de meeste hoogachting,

Johan VAN CALSTER
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Method of expressing the quantity of active ingredients in herbal medicinal products as presented in CTD, AMM, SPC, Package Insert and Labelling

1. INTRODUCTION

For herbal medicinal products, the whole herbal preparation in its entirety is recognized as the active ingredient.
According to the extent of which the herbal therapeutic active constituents are known, different types of herbs may be distinguished. These types are described in Section 2 of this document.
The aim of this document is to give some guidance in treating all herbal medicinal products concerning the aspect of the presentation of the quantitative composition.
The definitions of herbal drugs and related terms are given in the *Note for Guidance on Quality of Herbal Medicinal Products* [1] and in the *Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products* [2]. In addition, the following definition is used throughout the text:

Drug preparation ratio: The ratio between the herbal drug used and the quantity of native herbal preparation obtained
e.g.
- a drug preparation ratio of 5:1 means that 5 kg herbal drug was needed for the preparation of 1 kg native extract;
- a tincture has mostly a drug preparation ratio of 1:5 or 1:10.

For tinctures or liquid extracts, it is usually possible to keep tight limits on the drug preparation ratio; however, drug preparation ratios of dry extracts can vary depending of the quality of the herbal drug, as the extractible matter of a herbal drug is variable.

Herbal medicinal products could contain either the herbal drug or an herbal drug preparation.
- Section 3.1 describes herbal medicinal products composed of a herbal drug or a herbal drug preparation consisting of comminuted or powdered herbal drugs
- Section 3.2 describes herbal medicinal products composed of a herbal drug preparation produced by steps which exceed comminution

Throughout the text, reference is made to some sections of the CTD [3] in which some information should be given. The relevant sections used throughout this document are:

3.2.S Drug substance
3.2.S.2 Manufacture
3.2.S.2.6 Manufacturing process development
3.2.S.4 Control of Drug Substance

3.2.P Drug product
3.2.P.1 Description and Composition of the Drug Product
3.2.P.2 Pharmaceutical Development
3.2.P.5 Control of Drug Product
3.2.P.8 Stability of the Drug Product

2. TYPES OF HERBAL DRUGS, HERBAL DRUG PREPARATIONS AND HERBAL MEDICINAL PRODUCTS ACCORDING TO THE KNOWLEDGE OF THERAPEUTIC ACTIVE INGREDIENTS

According to the knowledge of the therapeutic active constituents, one can divide herbal drugs and the respective preparations into 3 classes.
Class A. Herbal drugs containing constituents (single or group) that are solely responsible for the acknowledged and documented therapeutic activity.
Standardisation to a defined content on these constituents is acceptable.
Medicinal products containing herbs of class A can be standardised by these constituents.

Class B. Herbal drugs of which all constituents responsible for the therapeutic activity are not known.
For herbal drugs of which the therapeutically active constituents are not known, the total plant material should be referred to in order to quantify the active material of the herbal medicinal product. To facilitate the analytics on the respective medicinal products, the concept **marker** has been defined [1,2]:
Markers are chemically defined constituents of a herbal drug which are of interest for control purposes independent of whether they have any therapeutic activity or not. Markers may serve to calculate the quantity of herbal drug or preparation in the finished product if that marker has been quantitatively determined in the herbal drug or preparation when the started materials are tested.

Class B1. Herbal drugs of which some but not all active constituents are known.
Therapeutic effects can be attributed to some (single or group) constituents; however, evidence that they are solely responsible for the clinical efficacy is not yet available. Herbs belonging to class B1 cannot merely considered as "without known therapeutically active constituents". Therefore, in addition to the concept of *total plant material = active substance*, a minimum limit on the content of the known therapeutic active matter is necessary. If appropriate (e.g. because of toxicity reason), a

maximum limit on the content of this active marker is incorporated too or upper and lower limits could be defined.
It is appropriate to use one or a class of the therapeutic active constituents as a marker, called **active marker.**

Class B2. Herbal drugs of which constituents documented as being determinant or relevant for efficacy are not known. The appropriateness of the choice of marker should be justified [2].

This classification has been used for the classification in the Ph. Eur. monograph "Extracts" (765) [4]:

1. Standardised extracts are adjusted within an acceptable tolerance to a given content of constituents with known therapeutic activity; standardisation is achieved by adjustment of the extract with inert material or by blending batches of extracts (Class A)
2. Quantified extracts are adjusted to a defined range of constituents; adjustments are made by blending batches of extracts (Class B1)
3. Other extracts are essentially defined by their production process (state of the herbal drug or animal matter to be extracted, solvent, extraction conditions) and their specifications (Class B2)

The classification of some herbal drugs is presented in Annex.

3. EXPRESSION OF THE QUANTITY OF ACTIVE INGREDIENT

1. Herbal medicinal products containing a herbal drug or a herbal drug preparation consisting of comminuted or powdered herbal drugs

Class A

The quantity of the herbal drug or the herbal drug preparation shall be given as a range corresponding to a defined quantity of constituents with known therapeutic activity [1].

Example for filing AMM, SPC and section 3.2.P.1 of CTD

Sennae folium	415 - 500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

Other information

The quantity of herbal drug or herbal drug preparation used should be justified in section 3.2.P.2, based on actual values found in different batches of the herbs. However, the quantity of plant material is not meant as taking part of the quantitative composition. It only gives some information on the reproducibility and reliability of the quality of the herb. Therefore, limits are usually rather wide.

In Part 3.2.P.5 and on the AMM, the limits on the active ingredients (= active constituents of the plant) are presented. Normally, 95.0 -105.0% is accepted, unless justified.

Class B2
The quantity of the herbal drug or the herbal drug preparation shall be stated if constituents with known therapeutic activity are unknown [1].

Example for filing AMM, SPC and section 3.2.P.1 of CTD

Valerianae radix (equivalent to dried herb) 900 mg

Other information
In this case, the marker may be used as an analytical tool by assaying it in the herb as well as in the herbal medicinal product. However, it cannot be presented on AMM or SPC.
In Part 3.2.P.5 and on the AMM, the limits on the active ingredients (= herbal drug) are given. Normally, 90.0 -110.0% is accepted, determined by weighing and/or assay of the marker.

It may be useful to give some limits on the assay of the marker in section 3.2.S.4, section 3.2.P.2 and/or section 3.2.P.5, based on actual values found in different batches. However, these limits will be rather wide and should be justified by actual values of the marker found in the plant material. This information can be used as a quality tool, demonstrating that the active ingredient used is of constant quality.

Class B1
The (group of) therapeutic active constituent(s) that are known are used as markers.

Examples for filing AMM, SPC and section 3.2.P.1 of CTD
1.

Hyperici herba (equivalent to dried herb) 1000 mg
(containing total hypericin, expressed as hypericin) (1.0 - 1.5 mg)

OR

Hyperici herba (equivalent to dried herb) 1000 mg
(containing 0.10 - 0.15% total hypericin, expressed as hypericin)

2.

Ginkgo folium (equivalent to dried herb) (containing total flavonoids, expressed as flavone glycosides)	500 mg (min. 1 mg)

OR

Ginkgo folium (equivalent to dried herb) (containing minimum 0.5% total flavonoids, expressed as flavone glycosides)	500 mg

If appropriate, for reasons of demonstrating a content of more than one therapeutically active (class of) constituent(s), 2 or more active markers can be used, e.g. containing 1.0 - 2.0 mg hypericin and minimum 25 mg hyperforin. The limits on active ingredient (= herbal drug, not the active marker) are normally accepted to be 90.0 - 110.0%.

Other information
The limit(s) on the assay of the active marker should be justified in section 3.2.S.4, section 3.2.P.2 and/or section 3.2.P.5, based on actual values found in different batches.

2. Herbal medicinal products containing herbal drug preparations as active substances

Class A

According to the *Note for Guidance on Quality of Herbal Medicinal Products* [1] if the constituents with known therapeutic activity are known, *the quantity of the herbal drug preparation may be given as a range corresponding to a defined quantity of these constituents*. The composition of any solvent or solvent mixture and the physical state of the extract must be indicated.

Example for filing AMM, SPC and section 3.2.P.1 of CTD

Sennae folium dry ethanolic extract 60% (V/V) [(3-7):1]	50 - 65 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

In Part 3.2.P.5 and on the AMM, the limits on the active ingredients (= active constituents of the plant) are presented. Normally, 95 -105% is accepted, unless justified.
If a diluent is used in the preparation of the extract, the quantity of the native extract should be used in the active constituents section, while the auxiliary substances should be presented in the "other components section" of the AMM.

Other information
As the constituents with known therapeutic activity are known, the herbal drug preparation is standardised by a defined quantity of constituents with known therapeutic activity, e.g. Senna extract 6% of hydroxyanthracene glycosides, calculated as sennoside B, with limits of 95.0 - 105.0%, unless justified. This should be described in Part 3.2.S.
The quantity of herbal drug used should be justified in section 3.2.S.2.6, based on actual values found in different batches of the herbs, corrected for loss on drying if appropriate. However, the quantity of plant material is not meant as taking part of the quantitative composition of the herbal plant preparation but can be considered as a quality issue, as it gives some information on the quality of the herb. Therefore, limits are usually rather wide.

Class B2

The equivalent quantity x - y, or the ratio (a - b): 1 of the herbal drug to the herbal drug preparation shall be stated if constituents with known therapeutic activity are unknown [1].

Example for filing AMM, SPC and section 3.2.P.1 of CTD

Valerianae radix dry extract ethanolic 60% (V/V) [(a - b): 1]	125 mg
OR	
Valerianae radix dry extract ethanolic 60% (V/V)	125 mg, equivalent to x - y mg Valerianae radix

In this case, a marker may be used as an analytical tool by assaying it in the herb as well as in the extract and in the herbal medicinal product. However, it cannot be presented on AMM or SPC.
In Part 3.2.P.5 and on the AMM, the limits on the active ingredients (= native extract) are given. Normally, 90 -110% is accepted, determined by assay of the marker in the herb and the herbal medicinal product.

Other information
The herbal drug preparation should be described in Part 3.2.S. As the constituents with known therapeutic activity are unknown, the herbal drug preparation *is essentially defined by its production process (state of the herbal drug … to be extracted, solvent, extraction conditions) and their specifications* [4].
The ratio herb to herbal preparation [(a - b): 1] should be justified in Section 3.2.S.2.6. The quantity (x - y) can logically be calculated from this ratio.
The choice of marker should be justified.
It may be useful to give some limits on the assay of the marker in the herbal drug as well as in the herbal drug preparation, based on actual values found in

different batches. However, these limits will be rather wide and should be justified by actual values of the marker found in the plant material. The information can be used as a quality tool, demonstrating that a reproducible and reliable quality of the plant as active ingredient is used.

Class B1

Example for filing AMM, SPC and section 3.2.P.1 of CTD

Hyperici herbae dry extract ethanolic 60% (V/V) [(a - b): 1]	200 mg
(containing total hypericin, expressed as hypericin)	(1.0 - 2.0 mg)

OR

Hyperici herbae dry extract ethanolic 60% (V/V)	200 mg, equivalent to x - y mg Hyperici herba
(containing total hypericin, expressed as hypericin)	(1.0 - 2.0 mg)

Analogous presentations with a percentage expression and/or only a minimum content, as shown in secton 3.1, Class B1, are possible.
The herbal drug preparation should be described in Part 3.2.S.
In Part 3.2.P.5 and on the AMM, the limits on the active ingredients (= native extract, not the active marker) are given. Normally, 90 -110% is accepted, determined by assay of the marker in the herb and the herbal medicinal product.

Other information
The ratio herb to herbal preparation [(a - b): 1] should be justified in Section 3.2.S.2.6. The quantity (x - y) can logically be calculated from this ratio.
The quantity of herbal drug used should be justified in section 3.2.S.2.6, based on actual values found in different batches of the herbs, corrected for loss on drying if appropriate.
The limits on the assay of the active marker should be justified in section 3.2.S.4, section 3.2.P.2 and/or section 3.2.P.5, based on actual values found in different batches.

3. Stability (Part 3.2.P.8)

In part 3.2.P.8 , it must be shown, as far as possible e.g. by means of appropriate fingerprint chromatograms, that all other substances present in the drug or in the herbal drug preparation are likewise stable and that their proportional content remains constant.

Depending on the type of herb used, the "other substances" are not always to be examined into the same depth. For Class A medicinal products, the assay of the known constituents are the most important ingredients and the examination of the other constituents is of less importance.
For Class B1, more attention has already to be paid to these other substances, together with the change in the concentration of the active markers.
For Class B2 products, the fingerprint chromatograms (TLC and/or HPLC and/or GC) are the most important means to determine the stability of the herbal finished product. The assay of the marker is one of the stability determining factors.
In the case that potential toxic constituents may arise on storage, special attention should be paid to them and limits should be fixed.

4. LITERATURE

1. Note for Guidance on Quality of Herbal Medicinal Products (CPMP/QWP/2819/00).
   http://www.emea.eu.int/pdfs/human/qwp/281900en.pdf
2. Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products (CPMP/QWP/2820/00).
   http://www.emea.eu.int/pdfs/human/qwp/282000en.pdf
3. CTD format, as accepted by the CPMP WPHMP (4-5 November 2002).
   http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctd_06-2004.pdf
4. Ph. Eur., Monograph "Extracts".
5. N. Brand, F. Gaedcke, L. Kabelitz and K.H.Sensch, Pharmeuropa, 12 (2), 265 (2000).
6. K. Helliwell, Pharmeuropa, 11 (4), 586 (1999).
7. R. Bauer, Drug Information Journal, 32, 101 (1998).
8. F. Lang and H. Stumpf, Pharmeuropa, 11 (2), 268 (1999).

ANNEXE: List of herbs, classified in A, B1 and B2

	Pharmacopoeial reference (if any)
Class A	
Frangulae cortex	Ph. Eur.
Hippocastani semen	DAB; Ph. Fr.
Liquiritia radix	Ph. Eur.
Rhamni purshianae cortex	Ph. Eur.
Rhei radix	Ph. Eur.
Sennae folium	Ph. Eur.
Silybi marianae semen	DAB
Class B1	
Foeniculi amari fructus	Ph. Eur.
Ginkgo folium	Ph. Eur.
Ginseng radix	Ph. Eur.
Glycine max L. herba et radix	-
Hyperici herba	Ph. Eur.
Matricariae flos	Ph. Eur.
Menthae piperitae folium	Ph. Eur.
Salicis cortex	Ph. Eur.
Thymi herba	Ph. Eur.
Zingiberis rhizoma	Ph. Eur.
Class B2	
Crataegi folium cum flore	Ph. Eur.
Crataegi fructus	Ph. Eur.
Harpagophyti radix	Ph. Eur.
Orthosiphonis folium	Ph. Eur.
Ribis nigri folium	-
Sabalis serrulatae fructus	Ph. Eur.
Urticae dioicae folium	-
Urticae dioicae radix	-
Valerianae radix	Ph. Eur.