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5 Committee on Herbal Medicinal Products (HMPC)

Guideline on quality of herbal medicinal products[2]/traditional herbal medicinal products

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[1] Previous document reference numbers: EMA/CPMP/QWP/2819/00, EMA/CVMP/814/00.
[2] Throughout the guideline and unless otherwise specified, the term “herbal medicinal product” (HMP) includes “traditional herbal medicinal product” (THMP).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Guideline on quality of herbal medicinal products/traditional herbal medicinal products

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Executive summary

This document intends to cover the general quality aspects of herbal medicinal products for human and veterinary use, including traditional herbal medicinal products for human use. It describes the special problems of herbal medicinal products and the differences between medicinal products containing chemically defined active substances.

Explanatory note on revision 1: This guideline updates the CPMP/CVMP/QWP 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products'. Further to the adoption of 'Directive 2004/24/EC for traditional herbal medicinal products for human use', the guideline was updated to take account of the newly introduced definitions and responsibilities. In addition, other clarifications and corrections to the existing text were introduced.

There is no expectation that existing herbal medicinal products (HMPs) on the market will be affected by this guideline, with the exception of traditional herbal medicinal products (THMPs) for human use that were already on the market on the entry into force of Directive 2004/24/EC (30 April 2004) for which the competent authorities shall apply the provisions of Directive 2004/24/EC within seven years of its entry into force. For any new marketing authorisation application, this guideline is applicable.

This guideline is also applicable to any traditional use (human) registration application submitted after 30 October 2005, by when, Member States shall comply with Directive 2004/24/EC.

Explanatory note on revision 2: Minor corrections updating the CPMP/CVMP/QWP 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' were introduced, which take into account new and revised guidelines, the European Pharmacopoeia revised general monograph 'Herbals Drugs', as well as new requirements for impurities. Given the nature of this update, a concept paper or public consultation was not required.

Explanatory note on revision 3: The third revision of the 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2819/00, EMA/CVMP/814/00, EMA/HMPC/201116/2005) takes into account new and revised guidelines, questions and answers and the European Pharmacopoeia revised general monograph 'Herbal Drug Extracts' as well as experiences gained over the years with the application of the guideline. Further clarifications on quality data requirements are provided via improved wording, structure and reference to updated related guidelines as outlined in the concept paper EMA/HMPC/217631/2015. Particular attention has been paid to adjustment with the in parallel revised Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and HMPs/THMPs (CPMP/QWP/2820/00; EMEA/CVMP/815/00, EMA/HMPC/162241/2005).

1. Introduction and legal basis

This guideline concerns the application of Module 3 of Annex I to Directive 2001/83/EC for human herbal medicinal products (HMPs) and Part 2 of Annex I to Directive 2001/82/EC for veterinary herbal medicinal products.

The special problems of HMPs and the differences between medicinal products containing chemically defined active substances[3] are described in this document. It should be read in conjunction with the

[3] The term ''active substance'' should be considered as equivalent to the terms ''active ingredient'' and ''drug substance''.

'Guideline on specifications: test procedures and acceptance criteria for herbal substances[4], herbal preparations[2] and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00, EMA/CVMP/815/00 and EMA/HMPC/162241/2005 as revised).

Directives 2001/83/EC and 2001/82/EC provide definitions for herbal substances, herbal preparations, and herbal medicinal products (HMPs). The basic legislation applies to HMPs for both human and veterinary use. An additional simplified registration procedure has been established for traditional herbal medicinal products (THMPs) for human use under Directive 2004/24/EC. According to these definitions a herbal medicinal product (HMP) is any medicinal product, exclusively containing as active ingredients 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. The quality of a HMP is independent of its traditional use, therefore all general principles of quality also apply to THMPs for human use. THMPs for human use may additionally contain vitamins and/or minerals. Concerning these products, this guideline describes specific aspects linked to mixtures of herbal substances/preparations with vitamins and/or minerals. In addition, the quality, specification and documentation for each vitamin and mineral have to comply with all relevant legislation and guidelines.

Applications should be submitted in the format referred to in the relevant Notice to Applicants, in the relevant volumes of the Rules Governing Medicinal Products in the European Union and the 'Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products' (EMA/HMPC/71049/2007 as revised).

The information on manufacture and control of the active substance (herbal substance and/or herbal preparation) may be supplied either as part of the marketing authorisation or registration application or by using the European Active Substance Master File (ASMF) procedure. If the latter route is chosen, the documentation should be submitted in accordance with the 'Guideline on active substance master file procedure' (EMEA/CPMP/QWP/227/02 and EMEA/CVMP/134/02 as revised).

Where the herbal preparation is the subject of a European Pharmacopoeia monograph, the EDQM Certification procedure PA/PH/CEP (02) 6 1R (for Certificates of Suitability: CEPs) can be used to demonstrate compliance with the relevant Ph. Eur. monograph.

2. Scope

This guideline intends to cover the general quality aspects of HMPs (for human and veterinary use), including THMPs for human use. Products containing chemically defined isolated constituents (irrespective of whether they are of natural or synthetic origin) or a mixture thereof are not HMPs.

For HMPs/THMPs, GMP recommendations should be respected. Under Article 16g, Articles 40 to 52 apply by analogy to HMPs. This includes Article 46 (f) of Directive 2001/83/EC which states that the Holder of a manufacturing authorisation shall at least be obliged to comply with the principles and guidelines of GMP for medicinal products and to use as starting materials only active substances, which have been manufactured with the detailed guidelines on GMP for active substances used as starting materials. Guidance is published in the "Manufacture of Herbal Medicinal Products" (The Rules Governing Medicinal Products in the European Union; Volume 4: EU Guidelines to Good Manufacturing Practice of Medicinal Products for Human and Veterinary Use; Annex 7).

Consistent quality for products of herbal origin can only be assured if the starting materials are defined in a rigorous and detailed manner, particularly the specific botanical identification of the plant material

[4] The terms "herbal substance" and "herbal preparation" should be considered as equivalent to the terms "herbal drug" and "herbal drug preparation" as defined in the European Pharmacopoeia.

used. It is also important to know the geographical source and the conditions under which the herbal substance is obtained to ensure material of consistent quality. The 'Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin (GACP)' (EMEA/HMPC/246816/2005) should also be applied.

3. Declaration of the active substance in the product information

The declaration of the active substance in the product information should be in line with the 'Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products' (EMA/HMPC/CHMP/CVMP/287539/2005 as revised).

4. Qualitative and quantitative particulars of the active substance(s) of a herbal medicinal product

4.1. Definitions

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

- **Standardised herbal substances / herbal preparations** are adjusted to a defined content of one or more *constituents with known therapeutic activity*. This is achieved by adjustment of the herbal substance/herbal preparation with inert excipients or by blending batches of the herbal substance/herbal preparation.

  Constituents with known therapeutic activity are chemically defined substances or groups of substances, which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a HMP.

- **Quantified herbal substances / herbal preparations** are adjusted to one or more *active markers*, the content of which is controlled within a limited, specified range. Adjustments are made by blending batches of the herbal substance/herbal preparation.

  Active markers are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

- **'Other' herbal substances / herbal preparations** are not adjusted to a particular content of constituents. For control purposes, one or more constituents are used as *analytical markers* that are determined quantitatively on a batch specific basis.

  Analytical markers are constituents or groups of constituents that serve for analytical purposes, irrespective of any pharmacological or therapeutic activity, which they may be reported to possess.

In cases where excipients for the manufacture of active substances are used (e.g. for technological reasons or for adjustment of standardised herbal substances/preparations), the name and the quantity of these excipients have to be defined.

For standardised herbal substances/herbal preparations (i.e. from herbal substances with constituents of known therapeutic activity), it should be stated how such standardisation is achieved. Suitable inert excipients may be added to adjust one or more constituents to a defined content. For quantified herbal substances/herbal preparations and 'other' herbal substances/herbal preparations, the addition of inert

excipients to adjust the content of assayed constituents is not permitted. Excipients can be included for technological reasons only and the content of such excipients must be stated as a fixed percentage. In some applications, an excipient may be added in a narrow percentage range (e.g. silicon dioxide between 0.1-0.5 per cent, to improve flowability of the extract). The proposed range must be justified by the manufacturer.

4.2. Herbal substances and herbal preparations consisting of comminuted or powdered herbal substances

For herbal substances and herbal preparations consisting of comminuted or powdered herbal substances the information should cover the name and the quantity of the herbal substance/herbal preparation together with the grade of comminution. Furthermore the following has to be indicated:

(i) In the case of standardisation: the quantity of the herbal substance/genuine preparation shall be given as a range corresponding to a defined quantity of constituents with known therapeutic activity.

(iia) In the case of quantification: the quantity of the herbal substance or the quantity of the genuine preparation shall be stated as a distinct content and the content of the active marker(s) shall be quantified in a range.

(iib) For all other cases: the quantity of the herbal substance or the quantity of the genuine herbal preparation shall be stated as a distinct content.

4.3. Herbal preparations produced by steps which exceed comminution

Herbal preparations can also be produced by steps which exceed comminution. Subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation leads to herbal preparations including extracts, tinctures, essential oils, expressed juices and processed exudates.

4.3.1. Extracts

In the case of extracts, the following has to be indicated:

(i) Standardised extracts: the equivalent quantity of the herbal substance x-y (*), or the ratio (a-b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation may be given as a range corresponding to a defined quantity of constituent(s) with known therapeutic activity.

(iia) Quantified extracts: the equivalent quantity of the herbal substance x-y (*), or the ratio (a-b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation has to be given as a distinct content. Furthermore, the content of the quantified active marker(s) shall be specified in a range.

(iib) 'Other' extracts: the equivalent quantity of the herbal substance x-y (*), or the ratio (a-b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation has to be given as a distinct content.

*) 'a' and 'b' or 'x' and 'y' have to be justified by the applicant.

The composition (nature and concentration(s)) of any extraction solvent or extraction solvent mixture and the physical state of the extract must be indicated.

If any other substance, e.g. an inert excipient to adjust a standardised preparation to a defined content of constituents with known therapeutic activity, or another excipient for any other purpose (e.g. technological excipients and suitable stabilisers, antioxidants, antimicrobial preservatives) is added during the manufacture of the herbal preparation, the added substance must be mentioned as an "excipient" and the genuine extract as the "active substance".

However, where different batches of the same extract are blended either to adjust constituents with known therapeutic activity to a defined content or for any other purpose, the final mixture of the genuine extracts shall be regarded as the genuine extract and listed as the "active substance" in the unit formula. Full details of production and control must however be provided in the dossier.

4.3.2. Herbal preparations produced by steps which exceed comminution not covered by 4.3.1

In the case of any other herbal preparation which is not an extract, the provisions of section 4.3.1 have to be applied accordingly, where applicable.

5. Description of the manufacturing process

5.1. Active substance

Appropriate information should be provided to adequately describe the manufacturing process of the active substance (herbal substance(s) and/or herbal preparation(s)). This should include details of the process together with the controls exercised and suitable validation data should be presented. The maximum holding time and storage conditions of bulk products should be stated and supported by appropriate validation data.

5.2. Herbal medicinal product

The manufacturing process, within the meaning of this section, is the preparation of the HMP from herbal substance(s) and/or herbal preparation(s). In the case of THMPs, the manufacturing process, within the meaning of this section, is the preparation of the HMP from herbal substance(s) and/or herbal preparations and may include the addition of vitamins and/or minerals.

The description should include details of the process together with the controls exercised. The maximum holding time and storage conditions of bulk products should be stated and supported by appropriate validation data. This section should be in accordance with the 'Guideline on manufacture of the finished dosage form' (EMA/CHMP/QWP/245074/2015 and EMEA/CVMP/126/95).

Information on development pharmaceutics and process validation should also be provided in accordance with the 'Note for guidance on development pharmaceutics' (CPMP/QWP/155/96), the 'ICH Guideline Q8 (R2) on pharmaceutical development' (EMA/CHMP/ICH/167068/2004), the 'Note for guidance: development pharmaceutics for veterinary medicinal products' (EMEA/CVMP/315/98) and 'Guideline on process validation for finished products - information and data to be provided in regulatory submissions' (EMA/CHMP/CVMP/QWP/BWP/70278/2012 as revised).

6. Control of starting materials for the manufacture of the herbal medicinal product / traditional herbal medicinal product

6.1. Control of herbal substances and of herbal preparations

This section should be in accordance with the 'Guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00 and EMA/CVMP/815/00 as revised).

6.1.1. Control of herbal substances

A comprehensive specification for each herbal substance must be submitted.

In the case of fatty or essential oils used as active substances of HMPs, a specification for the herbal substance is required unless justified (for details see: 'Reflection paper on quality of essential oils as active substances in herbal medicinal products/traditional herbal medicinal products' (EMA/HMPC/84789/2013). If fresh material is used and/or the oil production is linked to the collecting or harvesting processes, it is often difficult to establish a full analytical characterisation of the herbal substance. At least the identity of the herbal substance should be guaranteed, but other tests can be transferred to the essential oil (with reference to the Ph. Eur. monograph 'Herbal Drugs').

For each herbal substance, the binomial scientific name of the plant (genus, species, variety and author), chemotype (where applicable) and plant part have to be stated (Annex I of Directives 2001/83/EC or 2001/82/EC).

Detailed information on the site of cultivation/collection, the time of harvesting and stage of growth, treatment during growth with pesticides etc., and drying and storage conditions should be included. It should be confirmed that an adequate quality assurance system for the collection and/or cultivation, harvest and primary processing according to the 'Guideline on good agricultural and collection practice for starting materials of herbal origin' (GACP) (EMEA/HMPC/246816/05) is verified to be in place. A written GACP declaration for the herbal substance should be provided by the manufacturer of the active substance or the HMP, as appropriate.

If a monograph for a herbal substance exists in the European Pharmacopoeia (Ph.Eur.) or another Pharmacopoeia referred to in Annex I of Directives 2001/83/EC or 2001/82/EC, the herbal substance must be in accordance with this monograph.

If no monograph for the herbal substance is given in a Pharmacopoeia referred to in Annex I of Directives 2001/83/EC or 2001/82/EC, a comprehensive specification for the herbal substance must be developed which should be set out in the same way as the monographs on herbal drugs in the Ph. Eur. The comprehensive specification should be established on the basis of recent scientific data and in general give particulars of the characteristics, identification tests, assay and purity tests. Chromatographic fingerprinting should be used based on appropriate chromatographic methods. With regard to assay, the content of constituent(s) with known therapeutic activity or where constituents with known therapeutic activity are not known, marker substances, are required. The choice of markers should be justified (see EMA 'Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products' (EMA/HMPC/253629/2007)). In exceptional cases it may be acceptable to replace the assay by other tests (e.g. bitterness value, swelling index), based on appropriate limits.

As a general rule, herbal substances must be tested, unless otherwise justified, for microbiological quality, mycotoxins (aflatoxins, ochratoxin A), residues of pesticides and fumigation agents, heavy metals and likely contaminants (including heavy metals not mentioned in the monograph 'Herbal drugs' of the Ph. Eur. and contaminants present in the specific environment), foreign matter and adulterants, etc. If details on the collection site are limited, the potential for residues of pesticides and other contaminants should be fully addressed and where necessary appropriate screening techniques applied. The potential for pyrrolizidine alkaloid (PA) contamination, due, for example, to co-harvested/collected PA-containing plants, should be fully addressed. The need to control other potentially toxic contaminants from extraneous sources or specific conditions of processing (e.g. polycyclic aromatic hydrocarbons (PAHs) contamination) should also be considered. Unless otherwise fully justified, suitable validated methods should be used to control potential contaminants and the acceptance criteria should be justified. Radioactive contamination should be tested for if there are reasons for concern.

The use of ethylene oxide is prohibited for the decontamination of herbal substances[5].

Consideration on approaches to possible microbial decontamination of herbal substances and herbal preparations is given in the 'Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products' (EMA/HMPC/95714/2013).

Descriptions of the analytical procedures must be submitted, together with the limits applied. Analytical procedures not given in a Pharmacopoeia should be validated in accordance with the 'Note for guidance on validation of analytical procedures: Text and methodology' (CPMP/ICH/381/95), unless otherwise justified.

Reference materials of the herbal substances must be available for use in comparative tests e.g. macro- and microscopic examination, chromatography etc.

6.1.2. Control of herbal preparations

If the HMP contains a herbal preparation as active substance, rather than merely the herbal substance itself, the comprehensive specification for the herbal substance must be followed by information on the herbal preparation. A comprehensive specification from the manufacturer/marketing authorization holder for each herbal preparation must be submitted.

If a monograph for the herbal preparation exists in the Ph. Eur. or another Pharmacopoeia referred to in Annex I of Directives 2001/83/EC or 2001/82/EC, the herbal preparation would generally be in accordance with this monograph, taking into account the provisions of Ph. Eur. 5.23 (Monograph on Herbal Drug Extracts (Information Chapter)).

Where the herbal preparation is the subject of a European Pharmacopoeia monograph, the EDQM Certification procedure PA/PH/CEP (02) 6 1R (for Certificates of Suitability: CEPs) can be used to demonstrate compliance with the relevant Ph. Eur. monograph.

If no monograph for the herbal preparation is given in a Pharmacopoeia referred to in Annex I of Directives 2001/83/EC or 2001/82/EC, a comprehensive specification for the herbal preparation must be developed also taking into account the provisions of Ph. Eur. 5.23 (Monograph on Herbal Drug Extracts (Information Chapter))." This comprehensive specification should be established on the basis of recent scientific data and should, in general, give particulars of the characteristics, identification

[5] European Pharmacopoeia monograph on Herbal Drugs (1433)

tests, assay and purity tests. Chromatographic fingerprinting should be used based on appropriate chromatographic methods.

Tests on microbiological quality have to be included. If deemed necessary by analysis of the herbal substance being the starting material for the manufacture of the herbal preparation, tests on mycotoxins (aflatoxins, ochratoxin A), residues of pesticides and fumigation agents, toxic metals, and likely contaminants (including heavy metals not mentioned in the monograph 'Herbal drugs' of the Ph. Eur. and contaminants present in the specific environment), adulterants and solvents should be performed. The potential for pyrrolizidine alkaloid (PA) and polycyclic aromatic hydrocarbon (PAH) contamination should be fully addressed and controls applied, as needed, using suitable validated methods. Radioactivity should be tested for if there are reasons for concern.

A quantitative determination (assay) of constituent(s) with known therapeutic activity or of marker(s) is also required.

For **Standardised herbal preparations**, the content of constituent(s) with known therapeutic activity must be indicated with the lowest possible tolerance (with both upper and lower limits, e.g. x% ± y%)

For **Quantified herbal preparations**, the content of active marker(s) has to be given as a defined range.

For **'Other' herbal preparations**, for control purposes, one or more constituents are used as analytical markers and determined quantitatively within the acceptance criteria.

In general, acceptance limits for the content of a proposed marker should be specified and justified on the basis of the validated analytical range and historical data, if available (see 'Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products (EMEA/HMPC/253629/07)). In exceptional cases it may be acceptable to replace the assay by other tests (e.g. bitterness value, swelling index), based on appropriate limits.

Description of the analytical procedures with details of reference standards must be submitted, together with the limits applied. Analytical procedures not given in a Pharmacopoeia should be validated in accordance with the 'Note for guidance on validation of analytical procedures: Text and methodology' (CPMP/ICH/381/95), unless otherwise justified.

6.2. Control of vitamins and minerals (if applicable)

Vitamin(s) and mineral(s), which could be ancillary substances in THMPs for human use, should fulfil the requirements of all relevant legislation and guidelines.

6.3. Control of excipients

Excipients, including those added during the manufacture of the herbal preparations, should be described according to the 'Guideline on excipients in the dossier for application for marketing authorisation of medicinal products' (EMEA/CHMP/QWP/396951/2006), or the 'Note for guidance on excipients in the dossier for application for marketing authorisation of veterinary medicinal products' (EMEA/CVMP/004/98).

For solvents used in the manufacture of herbal preparations the 'Reflection paper on the use of recovered/recycled solvents in the manufacture of herbal preparations for use in herbal medicinal products/traditional herbal medicinal products' (EMA/HMPC/453258/2013) should be considered.

For novel excipients, the dossier requirements for active substances apply (refer to Directive 2001/83/EC for human medicinal products and Directive 2001/82/EC for veterinary medicinal products).

7. Control tests carried out at an intermediate stage of the manufacturing process of the herbal medicinal product

Details of all control tests, with details of test procedures and limits applied at any intermediate stages of the manufacturing processes and/or at stage of the bulk, are required especially if these tests cannot be performed on the HMP.

8. Control tests on the herbal medicinal product

This section should be in accordance with the 'Guideline on specifications and control tests on the finished product' (Eudralex 3AQ 11A), the 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00 and EMA/CVMP/815/00 as revised) and the analytical procedures should be validated according to the 'Note for guidance on validation of analytical procedures: Text and methodology' (CPMP/ICH/381/95).

The control tests on the finished product[6] should allow the qualitative and quantitative determination of the active substance(s) as well as the determination of characteristic properties of the dosage form and the entire finished product including packaging characteristics. Chromatographic fingerprinting should be used, based on appropriate chromatographic methods. A specification should be provided including tests for all relevant parameters.

In the case of HMPs containing as active substances herbal substance(s)/herbal preparation(s) with constituents of known therapeutic activity, these constituents should be specified and quantitatively determined. In general, the limits acceptable for the content of constituents with known therapeutic activity in the finished product at the time of release is the declared value ± 5%.

In the case of HMPs containing as active substances herbal substance(s)/herbal preparation(s) where the constituents with known therapeutic activity are not known, active or analytical markers should be specified and quantitatively determined. In general, the limits acceptable for the quantity of the genuine herbal preparation in the finished product at the time of release is the declared value ± 5%; if fully justified, a widening to maximum ± 10% of the declared value could be acceptable.

In exceptional cases it may be acceptable to replace the assay by other tests (e.g. bitterness value, swelling index), based on appropriate limits.

If a HMP/THMP contains a combination of several herbal substances and/or preparations as active substances, 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 approach should be justified, see 'Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products' (EMEA/HMPC/CHMP/CVMP/214869/2006).

For THMPs for human use containing vitamins and/or minerals, the vitamins and/or minerals should also be specified qualitatively and quantitatively determined.

[6] The term 'finished product'' should be considered as equivalent to the term ''drug product''.

The criteria given by the Ph. Eur. to ensure the microbiological quality should be applied unless justified. The frequency of testing for microbial contamination should be justified according to the 'Note for guidance on specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances' (CPMP/ICH/367/96) and 'Note for guidance on specifications: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: Chemical substances' (EMEA/CVMP/VICH/10/04).

9. Stability tests

9.1. General principles

This section should be in accordance with the 'Note for guidance on stability testing of new active substances and products' (CPMP/ICH/2736/99 as revised) and 'Guideline on stability testing of new veterinary drug substances and medicinal products' (CVMP/VICH/899/99 as revised), the 'Guideline on stability testing of existing active substances and related finished products' (CPMP/QWP/122/02 and EMEA/CVMP/846/99 as revised), the 'Note for guidance on in-use stability testing of human medicinal products' (CPMP/QWP/2934/99), the 'Note for guidance on in-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products)' (EMEA/CVMP/424/01) and Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/41500/2010 as revised).

The herbal substance/herbal preparation in its entirety is regarded as the "active substance''. For this reason, the basis for determining the stability of the herbal substance/herbal preparation and products thereof needs to be considered.

In cases where constituent(s) with known therapeutic activity are known and shown to be responsible for the overall effects of the herbal substance/herbal preparation, e.g. hydroxyanthracene derivatives, then stability testing of these constituents and their potential degradants will suffice.

However, in cases where the herbal substance/herbal preparation does not have constituent(s) with known therapeutic activity simply determining the stability of active marker(s) or analytical marker(s), will not suffice and a series of stability-indicating tests (eg. TLC, HPLC) will be needed. The stability of the herbal substance/herbal preparation as a multi-component system, should, as far as possible, also be demonstrated, e.g. by means of appropriate fingerprint chromatograms. It should also be demonstrated that their proportional content remains comparable to the initial chromatographic fingerprint.

Similarly, if more than one group of constituents is generally accepted to contribute to the therapeutic activity (quantified herbal substances/preparations) and/or if more than one group of constituents is of known relevance regarding quality, the chromatographic fingerprints should cover all relevant constituent groups.

Unless extensive degradation is expected during the first three months, it is considered acceptable to start the stability studies with a herbal substance/herbal preparation/HMP up to three months after the manufacturing date.

The testing frequency is set out in the 'Guideline on stability testing of existing active substances and related finished products' (CPMP/QWP/122/02 as revised).

9.2. Stability of herbal substances / herbal preparations

Testing at the accelerated storage condition or at the intermediate storage condition may be omitted for herbal substances/herbal preparations, if justified by the applicant and if the storage conditions below 25°C are clearly labelled.

Stress testing is usually considered unnecessary for herbal substances/herbal preparations except when, according to the toxicological assessment, toxic degradation products could appear.

Herbal substances which are used as starting materials in the manufacturing process for a herbal preparation shall comply with their specification immediately before use (e.g. before extraction).

Regarding the parameter content, specific characteristics of different types of herbal substances/herbal preparations should be taken into account.

Herbal substances / herbal preparations with constituents of known therapeutic activity:

The stability of the constituents with known therapeutic activity should be demonstrated, e.g. by means of appropriate fingerprint chromatograms of these constituents and an assay.

For stability studies of herbal substances/herbal preparations with constituents of known therapeutic activity, the results obtained for the content of these constituents must be compliant with the release acceptance criterion.

Herbal substances / herbal preparations for which constituents with known therapeutic activity are not known:

The stability of active marker(s) or analytical marker(s) should be demonstrated, e.g. by means of appropriate fingerprint chromatograms of these constituents and an assay.

Active markers

In the retest/shelf-life specification, a variation in active markers content of ± 5% from the initial value is acceptable. If fully justified, a widening to ± 10% from the initial content could be acceptable if it is ensured that also at the end of re-test/shelf-life the content is within the defined range.

Analytical markers

In the retest/shelf-life specification, a variation in analytical markers of ± 5% of the initial batch-specific value is acceptable. If justified, a widening to ± 10% from the initial batch-specific content could be acceptable. All analytical markers should remain within the release acceptance criteria, unless otherwise justified.

9.3. Stability of herbal medicinal products

Regarding the parameter content, specific characteristics of different types of herbal substances/herbal preparations used as active substances in HMP should be taken into account:

HMP containing, as active substances, herbal substances / herbal preparations with constituents of known therapeutic activity:

In the case of a HMP containing a herbal substance and/or a herbal preparation with constituent(s) of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed ± 5% of the declared assay value; in exceptional cases a widening to a maximum ± 10% of the declared content value may be acceptable with sufficient justification.

HMP containing, as active substances, herbal substances / herbal preparations for which constituents with known therapeutic activity are not known:

Active markers

During the proposed shelf-life the content of the active substance (calculated using one active marker) should remain within ± 5% of the initial value; if justified a widening to ± 10% from the initial value could be acceptable. All active markers should remain within ± 10% of the initial value and within the acceptance criteria ranges, unless otherwise justified.

Analytical markers

During the proposed shelf-life a variation of the batch-specific content of the analytical marker of ± 5% from the initial value is acceptable; a widening to ± 10% from the initial batch-specific content could be acceptable if justified.

For active or analytical markers, it is agreed that in some cases wider limits may be necessary, but the range should not be widened in general. Wider ranges can be accepted with adequate justifications. Different ranges for different markers in one active substance or one herbal medicinal product can be accepted.

If a HMP contains combinations of several herbal substances and/or herbal preparations, and if it is not possible to determine the stability of each active substance, the stability of the HMP should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical and sensory tests or other appropriate tests. The appropriateness of the tests shall be justified by the applicant in accordance to the 'Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products' (EMEA/HMPC/CHMP/CVMP/214869/06).

In the case of THMPs for human use containing vitamins and/or minerals, the stability of the vitamins and/or minerals should also be demonstrated.

10. Definitions

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Chromatographic fingerprinting: Application of chromatographic techniques to create a characteristic chromatographic pattern of phytochemical constituents which represents the multicomponent system typical of the herbal substance/herbal preparation/HMP.

Constituents with known therapeutic activity: are chemically defined substances or groups of substances, which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a HMP.

Drug extract ratio (DER): The ratio between the quantity of herbal drug (herbal substance) used in the manufacture of an extract and the quantity of extract obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal drug; the number written after the colon is the relative quantity of the extract obtained. Two DER can be distinguished:

- **Genuine (native) drug extract ratio ($DER_{genuine}$):** is the ratio between the quantity of herbal drug (herbal substance) used in the manufacture of an extract and the quantity of genuine (native) extract obtained.

- **Total drug extract ratio (DER_{total})**: is the ratio between the quantity of herbal drug (herbal substance) used in the manufacture of an extract and the quantity of whole extract (with excipients) obtained.

Extraction solvents: are solvents, which are used for the extraction process.

Genuine herbal preparation: refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.

Herbal drugs: The term herbal drug, used in European Pharmacopoeia, is synonymous with the term herbal substance used in European Community legislation on herbal medicinal products.

Herbal medicinal products (HMPs): 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.

Herbal preparations: are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Herbal substances: The term herbal substance is synonymous with the term herbal drug used in European Pharmacopoeia, All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Herbal teas: consist exclusively of one or more herbal substance(s) intended for oral aqueous preparations by means of decoction, infusion or maceration. The preparation is prepared immediately before use. Herbal teas are usually supplied in bulk form or in sachets.

Markers: are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the HMP if the marker has been quantitatively determined in the herbal substance or herbal preparation.

There are two categories of markers:

- **Active markers:** are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.
- **Analytical markers:** are constituents or groups of constituents that serve for analytical purposes, irrespective of any pharmacological or therapeutic activity, which they may be reported to possess.

Native herbal preparation: synonymous with **Genuine herbal preparation**

Quantification: means adjusting the herbal preparation to a defined range of constituents exclusively achieved by blending different batches of herbal substances and/or herbal preparations (e.g. quantified extracts).

Solvent: An inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a herbal preparation or the manufacture of a herbal medicinal product.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal preparation/herbal substance or HMP should conform to be considered acceptable for its intended use. "Conformance to specification" means that the herbal preparation/herbal substance and/or HMP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are legally binding quality standards that are proposed and justified by the manufacturer/marketing authorization holder and approved by regulatory authorities.

Standardisation: means adjusting the herbal substance/herbal preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts).

Traditional herbal medicinal products (THMPs): Medicinal products for human use that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC.

Types of herbal substances/herbal preparations:

- **Standardised herbal substances/herbal preparations** are adjusted to a defined content of one or more constituents with known therapeutic activity. This is achieved by adjustment of the herbal substance/herbal preparation with inert excipients or by blending batches of the herbal substance/herbal preparation.
- **Quantified herbal substances/herbal preparations** are adjusted to one or more active markers, the content of which is controlled within a limited, specified range. Adjustments are made by blending batches of the herbal substance/herbal preparation.
- **'Other' herbal substances/herbal preparations** are not adjusted to a particular content of constituents. For control purposes, one or more constituents are used as analytical markers.

11. References

Concept paper on the revision of the guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/217631/2015)

EDQM Certification procedure PA/PH/CEP (02) 6 1R (for Certificates of Suitability: CEPs)

Guideline on active substance master file procedure' (EMEA/CPMP/QWP/227/02 and EMEA/CVMP/134/02 as revised)

Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products' (EMA/HMPC/CHMP/CVMP/287539/2005 as revised).

Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin (GACP)' (EMEA/HMPC/246816/2005)

Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products' (EMEA/HMPC/CHMP/CVMP/214869/06)

Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products (CPMP/QWP/2820/00; EMEA/CVMP/815/00, EMA/HMPC/162241/2005 as revised).

Guideline on stability testing of existing active substances and related finished products (CPMP/QWP/122/02 and EMEA/CVMP/846/99 as revised)

Guideline on stability testing of new veterinary drug substances and medicinal products (CVMP/VICH/899/99 as revised)

Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products' (EMA/HMPC/71049/2007 as revised)

'Manufacture of Herbal Medicinal Products' in 'The Rules Governing Medicinal Products in the European Union; Volume 4: EU Guidelines to Good Manufacturing Practice of Medicinal Products for Human and Veterinary Use; Annex 7'

Monograph 'Herbal drug extracts' European Pharmacopoeia (0765).

Monographs on herbal drug extracts (Information chapter)' European Pharmacopoeia (5.23).

Note for guidance on in-use stability testing of human medicinal products' (CPMP/QWP/2934/99)

Note for guidance on in-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products)' (EMEA/CVMP/424/01)

Note for guidance on specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances' (CPMP/ICH/367/96)

Note for guidance on specifications: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: Chemical substances' (EMEA/CVMP/VICH/10/04)

Note for guidance on stability testing of new active substances and products' (CPMP/ICH/2736/99 as revised)

Questions & Answers on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/41500/2010 as revised)