EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 January 2022
EMA/HMPC/CHMP/CVMP/201116/2005[1] Rev. 3
Committee on Herbal Medicinal Products (HMPC)
Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

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

Final

Draft discussed by HMPC	January – July 2005
Draft agreed by Quality Working Party	June 2005
Draft adopted by CHMP for release for public consultation	27 July 2005
Draft adopted by CVMP for release for public consultation	13 July 2005
End of consultation (deadline for comments)	30 September 2005
Discussion in HMPC	November 2005 – January 2006
Adopted by HMPC	22 January 2006
Agreed by Quality Working Party	February 2006
Adopted by CHMP	23 March 2006
Adopted by CVMP	16 March 2006
Date for coming into effect	1 October 2006
Draft Revision 2 agreed by HMPC Quality Drafting Group	February 2011 April 2011
Revision 2 adopted by HMPC	31 March 2011
Revision 2 adopted by CHMP	12 September 2011

[1] Previous document reference numbers: EMA/CPMP/QWP/2819/00, EMA/CVMP/814/00 and EMA/HMPC/201116/2005 as revised.
[2] Throughout the guideline and unless otherwise specified, the term "herbal medicinal product" (HMP) includes "traditional herbal medicinal product" (THMP).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Revision 2 adopted by CVMP	14 September 2011
Draft Revision 3 agreed by HMPC Quality Drafting Group	19 April 2018
Draft Revision 3 adopted by HMPC for public consultation	05 June 2018
Draft Revision 3 agreed by Quality Working Party	30 June 2018
Draft Revision 3 adopted by CVMP	17 July 2018
Draft Revision 3 adopted by CHMP	26 July 2018
End of consultation (deadline for comments)	30 November 2018
Revision 3 adopted by HMPC	22 September 2021
Revision 3 agreed by Quality Working Party	23 November 2021
Revision 3 adopted by CHMP	17 January 2022
Revision 3 adopted by CVMP	18 January 2022

Table of contents

Table of contents 3

Executive summary 4

1. Introduction and legal basis 4

2. Scope 5

3. Qualitative and quantitative particulars of the active substance(s) of a herbal medicinal product 6

3.1. Definitions 6

3.2. Declaration of the active substance 7

3.2.1. Herbal substances and herbal preparations consisting of comminuted or powdered herbal substances 7

3.2.2. Herbal preparations produced by steps which exceed comminution 7

3.2.3. Extracts 7

3.2.4 Herbal preparations produced by steps which exceed comminution not covered by 3.2.3 8

4. Description of the manufacturing process 8

4.1. Active substance 8

4.2. Herbal medicinal product 9

5. Control of starting materials for the manufacture of the herbal medicinal product/traditional herbal medicinal product 9

5.1. Control of herbal substances and of herbal preparations 9

5.1.1. Control of herbal substances 9

5.1.2. Control of herbal preparations 10

5.2. Control of vitamins and minerals (if applicable) 12

5.3. Control of excipients 12

6. Control tests carried out at an intermediate stage of the manufacturing process of the herbal medicinal product 12

7. Control tests on the herbal medicinal product 12

8. Stability tests 13

8.1. General principles 13

8.2. Stability of herbal substances/herbal preparations 14

8.3. Stability of herbal medicinal products 15

9. Definitions 16

10. References 18

Executive summary

This document intends to cover the general quality aspects of herbal medicinal products (HMPs) for human and veterinary use, including traditional herbal medicinal products (THMPs) for human use. It describes the special problems of HMPs and the differences to 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". 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 HMPs on the market will be affected by this guideline, with the exception of 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 (Ph. Eur.) 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/HMPC/CHMP/CVMP/201116/2005 as revised) takes into account new and revised guidelines, questions and answers and the Ph. Eur. 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 herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/CHMP/CVMP/162241/2005 as revised). With regard to application to veterinary medicinal products the guideline has been aligned with Regulation (EU) 2019/6 on veterinary medicinal products.

This guideline shall be read in conjunction with the applicable legislation for human and veterinary medicinal products respectively.

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 the dossier as established by Commission Delegated Regulation (EU) 2021/805 amending Annex II of Regulation (EU) 2019/6 for veterinary medicinal products.

The special problems of HMPs and the differences to medicinal products containing chemically defined active substances[3] are described in this document. It should be read in conjunction with the "Guideline on specifications: test procedures and acceptance criteria for herbal substances[4], herbal preparations and herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/CHMP/CVMP/162241/2005 as revised).

Directive 2001/83/EC provides definitions for herbal substances, herbal preparations, herbal medicinal products (HMPs) and traditional herbal medicinal products (THMPs). 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.

Regulation (EU) 2019/6 on veterinary medicinal products does not include a specific definition or any specific provisions for herbal veterinary medicinal products and their authorisation. However, Article 4 of the Regulation (EU) 2019/6 includes vegetable origin as one of the potential sources of an active substance and recital (12) of the preamble and respective Article 157 note that a simplified system for the registration of traditional herbal products used to treat animals in the Union would be premature until a Commission report on this matter is delivered.

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 should comply with all relevant legislation and guidelines.

Applications for medicinal products for human use should be submitted in the format referred to in the Notice to Applicants for human medicinal products, 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). For herbal veterinary medicinal products, the dossier should follow the structure and content requirements established in Annex II to Regulation (EU) 2019/6, as amended by Commission Delegated Regulation (EU) 2021/805, Section II.

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 (where applicable) 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" (CHMP/QWP/227/02 and EMEA/CVMP/134/02 as revised).

Where the herbal preparation is the subject of a European Pharmacopoeia (Ph. Eur.) 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.

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

For HMPs, GMP recommendations should be respected. For human products - under Article 16(g) of Directive 2001/83/EC, Articles 40 to 52 apply by analogy to THMPs. 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 only active substances, which have been manufactured with the detailed guidelines on GMP for active substances. For veterinary medicinal products, in accordance with Article 93(1)(j) of Regulation (EU) 2019/6 manufacturing authorisation holders shall comply with GMP for veterinary medicinal products and only use active substances that comply with GMP for active substances. 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 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 (GACP) for starting materials of herbal origin" (EMEA/HMPC/246816/2005) should also be applied.

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

3.1. 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:

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:

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 should 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. to improve flowability, compressibility or solubility of the extract. The proposed range must be justified by the manufacturer.

3.2. Declaration of the active substance

The declaration of the active substance in the documentation and 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).

3.2.1. 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.

3.2.2. 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.

3.2.3. 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.

3.2.4. Herbal preparations produced by steps which exceed comminution not covered by 3.2.3

In the case of any other herbal preparation which is not an extract, the provisions of section 3.2.3 should be applied accordingly, where applicable.

4. Description of the manufacturing process

4.1. 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. Data on manufacturing process development should be added, if available. The maximum holding times and storage conditions applied during the manufacturing process should be defined, if applicable.

The selection of a decontamination process should be fully justified on the basis of the type and composition of the herbal material, its intended use and route of administration. The use of ethylene oxide is prohibited for the decontamination of herbal substances[5].

Any use of recovered/recycled solvent should be justified.

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

4.2. 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 THMP 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 intermediate and bulk products should be stated and supported by stability data. This section should be in accordance with the "Guideline on manufacture of the finished dosage form" (EMA/CHMP/QWP/245074/2015) and "Guideline on manufacture of the veterinary finished dosage form" (EMA/CVMP/QWP/798401/2015).

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).

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

5.1. 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/HMPC/CHMP/CVMP/162241/2005 as revised).

5.1.1. 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. 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. While at least the identity of the herbal substance should be ensured, 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 has to be stated (Annex I of Directive 2001/83/EC). With regards to veterinary medicinal products the usual terminology as indicated in Annex II to Regulation (EU) 2019/6, as amended, Section II.2A1(2), should be followed. This is expected to result in inclusion of the same information for human and veterinary herbal medicinal products.

Information on the site of cultivation/collection, the time of harvesting and stages of growth, treatment during growth with pesticides etc., and drying and storage conditions should be included. The origin should be stated at least on country level. 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 (GACP) for starting materials of herbal origin" (EMEA/HMPC/246816/05) is in place at these stages of process. A written GACP confirmation for the herbal substance should be provided by the herbal substance supplier, 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 Directive 2001/83/EC or in Annex II of Regulation (EU) 2019/6, as amended, 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 Directive 2001/83/EC or in Annex II of Regulation (EU) 2019/6, as amended, 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.[6] 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. 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.

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), for human medicinal products, and VICH GL1 and VICH GL2 on validation of analytical procedures (CVMP/VICH/590/98 and CVMP/VICH/591/98) for veterinary medicinal products, 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.

5.1.2. 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

[6] For guidance see https://www.edqm.eu/sites/default/files/medias/fichiers/European_Pharmacopoeia/Find_information_on/Technical_Guides/Technical_Guide_for_the_Elaboration_of_Monographs_on_herbal_drugs_and_herbal_drug_preparations_2007.pdf

herbal preparation. A comprehensive specification from the manufacturer/marketing authorisation/registration 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 Directive 2001/83/EC or in Annex II of Regulation (EU) 2019/6, as amended, the herbal preparation would generally be in accordance with this monograph, taking into account the provisions of Ph. Eur. 5.23 monographs on herbal drug extracts (information chapter).

Where the herbal preparation is the subject of a Ph. Eur. 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 Directive 2001/83/EC or in Annex II of Regulation (EU) 2019/6, as amended , a comprehensive specification for the herbal preparation must be developed also taking into account the provisions of Ph. Eur. 5.23 monographs on herbal drug extracts (information chapter)[6]. This comprehensive specification should be established on the basis of recent scientific data and should, in general, give particulars of the characteristics, identification tests, assay and purity tests. Chromatographic fingerprinting should be used based on appropriate chromatographic methods.

Tests on microbiological quality should 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 considered and controls applied, as needed, using suitable validated methods. It is the responsibility of the applicant to justify at which stage testing of such impurities takes place. In any event, the chosen acceptance criteria should be justified and the final posology of the HMP should be taken into account in controls to be applied on, when necessary, e.g. for PAs.
A test for radioactivity should be included 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. Specific requirements of Ph. Eur. and EU herbal monographs should be considered, if applicable. 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) for human medicinal products, and VICH GL1 and VICH GL2 on

validation of analytical procedures (CVMP/VICH/590/98 and CVMP/VICH/591/98) for veterinary medicinal products, unless otherwise justified.

5.2. 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.

5.3. 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 novel excipients in human medicinal products, the dossier requirements for active substances apply (refer to Directive 2001/83/EC). For novel excipients in veterinary medicinal products details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non- clinical, shall be provided. For colouring matters the declarations of compliance as mentioned under Part II.2C2, points (3) and (4) shall be considered sufficient (refer to Annex II of Regulation (EU) 2019/6, as amended).

6. 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.

7. 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/HMPC/CHMP/CVMP/162241/2005 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) or – for veterinary medicinal products – with VICH GL1 and VICH GL2 on validation of analytical procedures (CVMP/VICH/590/98 and CVMP/VICH/591/98).

The control tests on the finished product[7] 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.

Contaminants should be considered. For elemental impurities, the principles of ICH Q3D for human medicinal products and Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/153642/2018) should be applied. It is the

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

responsibility of the applicant to justify at which stage testing of such impurities takes place. In any event, the chosen acceptance criteria should be justified and the controls to be applied should take account of current limits of intake and the final posology of the HMP.

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 justified, a widening up to ± 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.

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 specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances" (CPMP/ICH/367/96) and "Guideline on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances" (EMEA/CVMP/VICH/810/04).

8. Stability tests

8.1. General principles

This section should be in accordance with the "Note for guidance on stability testing of new drug 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/QWP/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, stability testing of these constituents and their potential degradants, if toxicologically relevant, 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 (e.g. 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.

In line with the release specification, the assay may in exceptional cases be replaced by other tests (e.g. bitterness value, swelling index) based on appropriate limits.

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.

It is considered acceptable to start the stability studies with an herbal substance/herbal preparation/HMP up to three months after the manufacturing date. However, in case extensive instability occurs during the first three months, start of the stability studies 3 months after the manufacturing date is not acceptable.

The testing frequency is set out in the "Guideline on stability testing of existing active substances and related finished products" (CPMP/QWP/122/02 and EMEA/CVMP/QWP/846/99 as revised).

8.2. 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 the specification before use (e.g. before extraction). For herbal substances which are used as active substances of HMPs, appropriate stability testing has to be performed.

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 the active markers content of ± 5% from the initial batch-specific value is acceptable. If justified, a widening up to ± 10% from the initial batch-specific content could be acceptable. In any case, it has to be ensured that at the end of re-test/shelf-life, the contents for all the active markers remain within the defined ranges.

Analytical markers

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

8.3. Stability of herbal medicinal products

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

HMPs 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.

HMPs 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 up to ± 10% from the initial value could be acceptable. All active markers should remain within ± 5% of the initial value; if justified a widening to ± 10% from the initial value could be acceptable.

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 up 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 than ± 10 % 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 HMP 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 with 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.

9. 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 (Ph. Eur.), is synonymous with the term herbal substance used in European Union 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 (Ph. Eur.). 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 authorisation holder/registration 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.

10. References

Directive 2001/83/EC on the Community code relating to medicinal products for human use

Regulation (EU) 2019/6 on veterinary medicinal products

Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6

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)

EDQM Technical guide on elaboration of monographs. Available at: https://www.edqm.eu/sites/default/files/medias/fichiers/European_Pharmacopoeia/Find_information_on/Technical_Guides/Technical_Guide_for_the_Elaboration_of_Monographs_on_herbal_drugs_and_herbal_drug_preparations_2007.pdf

Guideline on active substance master file procedure (CHMP/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 (GACP) for starting materials of herbal origin (EMEA/HMPC/246816/2005)

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

Guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015)

Guideline on manufacture of the veterinary finished dosage form (EMA/CVMP/QWP/798401/2015)

Note for guidance on development pharmaceutics (CPMP/QWP/155/96)

ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/ICH/167068/2004)

Note for guidance: development pharmaceutics for veterinary medicinal products (EMEA/CVMP/315/98)

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)

Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/162241/2005 as revised)

Note for guidance on validation of analytical procedures: text and methodology (CPMP/ICH/381/95)

VICH GL1 and VICH GL2 on validation of analytical procedures (CVMP/VICH/590/98 and CVMP/VICH/591/98)

Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006)

Note for guidance: excipients in the dossier for application for marketing authorisation for veterinary medicinal products (EMEA/CVMP/004/98)

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

Guideline on stability: 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)

ICH guideline Q3D (R1) on elemental impurities (EMA/CHMP/ICH/353369/2013)

Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/153641/2018)

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

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)

Guideline on specifications and control tests on the finished product (Eudralex 3AQ 11A)

Note for guidance specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances (CPMP/ICH/367/96)

Guideline on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances (EMEA/CVMP/VICH/810/04)

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

Ph. Eur. monographs on herbal drug extracts (information chapter) (5.23)

Ph. Eur. monograph on herbal drug extracts (0765)

Reflection paper on the use of fumigants (EMEA/HMPC/125562/2006)

Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products (EMEA/HMPC/253629/2007)

Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products (EMA/HMPC/95714/2013)

Reflection paper on quality of essential oils as active substances in herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/84789/2013)

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)

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