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Guideline on specifications: test procedures and acceptance criteria for herbal substances[2], herbal preparations[3] and herbal medicinal products[4]/traditional herbal medicinal products

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[2] The term "herbal substance" should be considered as equivalent to the term "herbal drug" as defined in the European Pharmacopoeia.
[3] The term "herbal preparation" should be considered as equivalent to the term "herbal drug preparation" as defined in the European Pharmacopoeia.
[4] Throughout the guideline and unless otherwise specified, the term "herbal medicinal product" (HMP) includes "traditional herbal medicinal product" (THMP).

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Executive summary

This document addresses specifications, i.e. those tests, procedures, and acceptance criteria used to assure the quality of the herbal substances/preparations and herbal medicinal products – both human and veterinary ones (HMPs) at release and during the shelf-life.

Explanatory note on revision 1: This guideline updates the CPMP/CVMP/QWP "Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and 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 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 specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and 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 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) takes into account new and revised guidance documents such as the updated "Questions & Answers on quality of HMPs/THMPs" (EMA/HMPC/41500/2010), the Ph. Eur. revised general text on the "microbiological quality of herbal medicinal products for oral use and extracts used in their preparation" (5.1.8), the revised general Ph. Eur. monograph "Herbal Drug Extracts" and the new information chapter on this monograph, the "Guideline on quality on combination HMPs/THMPs" (EMEA/HMPC/CHMP/CVMP/214869/2006) and the "Reflection paper on markers used for quantitative and qualitative analysis of HMPs/THMPs" (EMEA/HMPC/253629/2007) as outlined in the Concept paper EMA/HMPC/217753/2015. Particular attention has been paid to adjustment with the in parallel revised "Guideline on quality of herbal medicinal products /traditional herbal medicinal products" (EMA/HMPC/CHMP/CVMP/201116/2005 as revised). With regard to application to veterinary medicinal products the guideline has been aligned with Regulation (EU) 2019/6 on veterinary medicinal products.

1. Introduction and legal basis

1.1. Objective of the guideline

This guidance document provides general principles on the setting and justification, to the extent possible, of a uniform set of specifications for herbal substances/preparations and herbal medicinal products (HMPs) to support applications for marketing authorisation or registration (HMPs for human use only) according to Directive 2001/83/EC (HMPs for human use) and Regulation (EU) 2019/6

(veterinary HMPs) respectively. It should be read in conjunction with the "Guideline on quality of herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/CHMP/CVMP/201116/2005 as revised).

A simplified registration procedure was established for THMPs for human use under Directive 2004/24/EC. 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/herbal 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.

1.2. Background

A specification is defined as a list of tests, references to analytical and biological 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 substance/preparation or HMP should conform to be considered acceptable for its intended use. "Conformance to specification" means that the herbal substance/preparation 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/registration holder and approved by regulatory authorities.

Specifications are one part of a total control strategy for the herbal substance/preparation and HMP designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterisation during development, upon which specifications are based, adherence to the "guideline on good agricultural and collection practice (GACP)" (EMEA/HMPC/246816/2005) and good manufacturing practice (GMP), and a validated manufacturing process, validated test procedures, e.g. raw material testing, in-process testing, stability testing, etc.

In the case of HMPs, specifications are generally applied to the herbal substance, the herbal preparation and the HMP. Specifications are primarily intended to define the quality of the herbal substance/preparation and HMP rather than to establish full characterisation. They should focus on those characteristics found to be useful in ensuring the safety and, if appropriate, efficacy of the herbal substance/preparation and HMP.

In contrast to medicinal products containing chemically defined active substances[5], for HMPs that contain herbal preparations as active substances, a specification is also necessary for the herbal substance, even when the herbal substance serves solely as a starting material for the herbal preparation and not as the active substance itself.

2. Scope

The quality of herbal substances, herbal preparations and HMPs is determined by the quality of the starting plant material, development, in-process controls, GMP controls and process validation, and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, i.e. those tests, procedures, and acceptance criteria used to assure the quality of the herbal substances/preparations as well as of HMPs at release and during the shelf-life. Specifications are an important component of quality assurance but are not its only component. The consideration of

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

all aspects listed above is necessary to ensure the consistent production of herbal substances/preparations and HMPs of high quality.

This guideline addresses only the marketing approval of HMPs (including fixed combinations); it does not address herbal substances/preparations or HMPs during the clinical research stages of product development but should be viewed as useful points for consideration.

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.

Guidance is provided with regard to specifications, which should be established for all herbal substances/preparations and HMPs, i.e. universal tests and acceptance criteria, and those, which are considered specific to individual herbal substances/preparations and/or dosage forms. This guideline reflects the current state of the art at the time it has been written and should not be considered all encompassing. New analytical technologies, and modifications to existing technologies, are continuously being developed. Such technologies should be used when appropriate.

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

3. General concepts

The following concepts are important in the development and setting of specifications. They are not universally applicable, but each should be considered in particular circumstances. This guideline presents a brief definition of each concept and an indication of the circumstances under which it may be applicable. Generally, proposals to implement these concepts should be justified by the applicant and approved by the appropriate regulatory authority before being put into effect.

3.1. Characterisation and assay

Consistent quality for products of herbal origin can only be assured if the starting plant materials are defined in a rigorous and detailed manner. Characterisation of a herbal substance/herbal preparation or HMP (which includes a detailed evaluation of the botanical and phytochemical aspects of the herbal substance, manufacture of the herbal preparation and the HMP) is therefore essential to allow specifications to be established, which are both comprehensive and relevant.

Acceptance criteria should be established and justified based on information from batches used in pre-clinical/clinical studies or described in relevant bibliographic data, and if relevant, published information concerning biological variation, where available. Data from batches used to demonstrate manufacturing consistency, relevant development data, such as those arising from analytical procedures and stability studies, as well as historical batch data, should be taken into account, where available.

Extensive characterisation is usually performed only in the development phase and, where necessary, following significant process changes. At the time of submission, the manufacturer should have established appropriately characterised in-house reference materials (primary and working), which will serve for identification and determination of content of production batches.

3.1.1. Identification

3.1.1.1. Macroscopical/microscopical characterisation

Includes features, which characterise the herbal substance and serve for identification purposes and to distinguish it from potential adulterants and substitutes.

3.1.1.2. Phytochemical characterisation

Includes analytical data, such as chromatographic fingerprinting, on constituents with known therapeutic activity, on compounds suitable as active markers or analytical markers as well as other constituents.

Chromatographic fingerprinting is an analytical technique which serves as a valuable tool to characterise herbal substances/herbal preparations/HMPs. In HMPs, the herbal substance/herbal preparation in its entirety is regarded as the active substance as a complex multi-component system. Characteristic constituents are selected as specific for the herbal substance/herbal preparation and serve as phytochemical fingerprints for quality control purposes. Chromatographic fingerprinting is used for identity testing as well as during stability testing.

In the release specification chromatographic fingerprinting is used for identification of the herbal substance/herbal preparation and HMP. It should also be included in the re-test/shelf-life specification of the herbal preparation and HMP, as appropriate, to demonstrate consistent quality.

During stability testing the fingerprint chromatogram should be comparable to the fingerprint at the initial time point.

3.1.2. Impurities

Impurities can generally be classified as follows:

- impurities arising from starting materials (active substances, excipients) and containers;
- process related impurities arising from the manufacturing process.

For HMPs, particular issues arise due to the origin of the herbal substances and the following groups of impurities should be addressed, as appropriate:

Contaminants, which include impurities such as heavy metals and other elemental impurities (ICH Q3D and Reflection paper on elemental impurities EMA/CVMP/QWP/153642/2018), residues of pesticides and fumigants, mycotoxins (aflatoxins, ochratoxin A), microbial contamination, pyrrolizidine alkaloids (PAs) and radioactive substances, if relevant. The need to control other potentially toxic contaminants from extraneous sources (e.g. polycyclic aromatic hydrocarbons (PAHs) contamination) should also be considered.

Degradation products, which in the context of this guideline, due to the particular nature of HMPs, should primarily address toxicologically relevant impurities arising from degradation of herbal substances/preparations.

Absence or accepted levels of known toxic relevant degradation products in the herbal substance/herbal preparation/HMP should be determined.

Residual solvents, which are impurities arising from manufacturing processes.

3.1.3. Assay

For the purposes of quality control, the specification for the herbal substance/herbal preparation and HMP should, as a general rule, include an assay. The choice of constituent(s) to be assayed depends on whether or not the herbal substance/herbal preparation/HMP contains constituents with known therapeutic activity. Where constituents with known therapeutic activity are not present then markers are used for identification and quantification of herbal substance(s)/herbal preparation(s) and HMPs. In exceptional cases it may be acceptable to replace the assay by other tests (e.g. bitterness value and swelling index).

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.

In general, the content of active substance in the finished product[6] at release should be specified at ± 5% of the declared content (Guideline on specifications and control tests on the finished product (Eudralex 3AQ 11A) and Annex II to Regulation (EU) 2019/6, as amended by Commisision Delegated Regulation (EU) 2021/805).

Constituents with known therapeutic activity are known:

Where the herbal substance(s)/herbal preparation(s) contain constituents with known therapeutic activity and thus fall within Standardised *herbal substances/herbal preparations,* these constituents should be specified and quantitatively determined. The content of these constituents should be compliant with the release acceptance criterion.

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%. The variation in content during the proposed shelf-life should not exceed ± 5% of the declared value; in exceptional cases a widening to maximum ± 10% of the declared value may be acceptable with sufficient justification.

Constituents with known therapeutic activity are not known:

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 the herbal substance, herbal preparation and HMP. The choice of such markers should be justified. The batch-specific content of the marker(s) should enable the quantification of the herbal substance/herbal preparation as active substance in the finished product. In general, the limits acceptable for the quantity of the active substance in the finished

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

product at the time of release is the declared value ± 5%; if 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.

Choice and use of markers:

In the view of the specific and complex nature of HMPs, markers can provide an option to demonstrate the quality of these products.

Selection of markers should be justified. Markers should be suitable for their intended purpose (e.g. identification, quantification, analytical control, stability).

Where the herbal substance is the subject of a monograph of the Ph. Eur. or of another Pharmacopoeia referred to in Annex I of Directive 2001/83/EC or in Annex II to Regulation (EU) 2019/6, as amended, the herbal substance should be assayed using the constituents given in the definition of the monograph.

Active markers:

The content of active markers in quantified active substance has to be specified in a range which has to be justified (e.g. by compliance with a Ph. Eur. monograph or batch data). The defined range for each active marker has to be included in the release and re-test/shelf-life specification, as appropriate. Additionally, in the re-test/shelf-life specification, a variation in each active marker content of ± 5% from the initial value is acceptable. If justified, a widening to ± 10% from the initial content could be acceptable. In any case, it has to be ensured that also at the end of re-test/shelf-life, the content for all the active markers remains within the defined ranges.

In the release specification of the finished product the content of the active substance should be calculated using one of the active markers and should be set to ± 5% of the declared content. All the active markers should be within ± 5% of the declared ranges. During the proposed shelf-life the content of the active substance (calculated using the selected 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 up to ± 10% from the initial value could be acceptable. However, 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.

Analytical markers:

Analytical markers serve for analytical purposes where constituents with known therapeutic activity are not known and there are no active markers. The batch-specific content should enable the batch specific quantification of the active substance (e.g. "other extract") in the finished product and should contribute, together with other analytical methods, to the estimation of the stability of the active substance and of the finished product.

If the constituent described for assay in the monograph of Ph. Eur. or in another Pharmacopoeia referred to in Annex I of Directive 2001/83/EC or in Annex II of Regulation (EU) 2019/6, as amended is not considered suitable as an analytical marker (e.g. not stable in the herbal preparation or the finished product; not quantifiable due to limitations in the validation of the assay in the finished product), it may be acceptable to substitute it by an alternative marker. The use of the alternative marker should be justified. In any case, the same analytical marker for release and stability testing

should be used, in exceptional cases different markers can be accepted where justified on the basis of analytical data.

The content of an analytical marker in an active substance has to be determined quantitatively within the acceptance criteria. The acceptance criteria defined in the release specification should be justified on the basis of relevant bibliographic data, especially published information concerning biological variation and data from batches used to demonstrate manufacturing consistency, relevant development data, such as the results of validation of the analytical procedure. 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. or EU herbal monographs should be considered, if applicable.

In the re-test/shelf-life specification, as appropriate, a deviation 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.

The amount of the active substance in the finished product should be calculated using the batch-specific content of the analytical marker. 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. However, it is agreed that in some cases wider limits may be necessary, but the range should not be widened in general. Wider ranges than ± 10 % can be accepted with adequate justifications. Different ranges for different markers in one active substance or one herbal medicinal product can be accepted.

3.2. Periodic/skip testing

Periodic or skip testing is the performance of specified tests at release on pre-selected batches and/or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still should meet all acceptance criteria established. This represents a less than full schedule of testing and should therefore be justified and presented to the regulatory authority prior to implementation.

Periodic/skip testing can only be applied if justified, based on data and with a risk assessment approach and a pre-defined testing scheme.

3.3. Release versus shelf-life tests and acceptance criteria

The establishment of different tests and different acceptance criteria for the re-testing of a herbal substance, herbal preparation/shelf-life of HMP, than those applied at release is acceptable, if justified.

For the chromatographic fingerprint, during the shelf-life and re-test periods, this should remain comparable to the chromatogram at the initial time point.

For the parameter assay, different acceptance criteria for release and shelf-life may be acceptable (see above).

This concept may also be applicable to impurity limits (degradation products).

3.4. In-process controls

In-process controls are tests, which are performed during the manufacture of either the herbal preparation or HMP, rather than as part of the formal battery of tests, which are conducted prior to release. In-process controls, which are used for the purpose of adjusting process parameters within an

operating range, e.g. hardness and friability of tablet cores which will be coated, are not included in the specification. Certain tests conducted during the manufacturing process, where the acceptance criteria are identical to or tighter than the release requirement (e.g. pH of a solution), may be used to satisfy specification requirements when the test is included in the specification.

3.5. Design and development considerations

The experience and data accumulated during the development of a herbal substance/preparation or HMP should form the basis for the setting of specifications. In general, it is only necessary to test the HMP for quality attributes uniquely associated with the particular dosage form and the herbal substance or herbal preparation present.

3.6. Pharmacopoeial tests and acceptance criteria

The European Pharmacopoeia (Ph. Eur.) contains monographs describing analytical procedures and acceptance criteria to define the quality of herbal substances and herbal preparations and general tests for HMPs.

Wherever they are appropriate, pharmacopoeial procedures should be utilised and are accepted to demonstrate compliance to a monograph. With the agreement of the competent authority, alternative procedures to pharmacopoeial procedures may be used to test the quality of the herbal substance/preparation, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In case of doubt or dispute, the methods of analysis of the Pharmacopoeia are authoritative.

For a herbal substance/herbal preparation, if a monograph is given in the Ph. Eur. or in another Pharmacopoeia referred to in Annex I of Directive 2001/83/EC or in Annex II of Regulation (EU) 2019/6, as amended , the quality of the herbal substance/herbal preparation should be specified in accordance with this monograph.

For a herbal substance where the monograph of the herbal substance does not include an assay, the applicant is not required to develop an assay. If no monograph for the herbal substance is given in a Pharmacopoeia, the applicant is required to develop a comprehensive specification including testing of identity, purity and a suitable assay, unless otherwise justified.

For a herbal preparation, if the monograph of the herbal preparation does not include an assay, applicants are not required to develop an (specific) assay, e.g. Cinnamon, Myrrh, Gentian tinctures.

However, because it is a legal requirement that the content of the active substance is determined quantitatively in the finished product, an assay is normally needed to calculate the declared content of the active substance in the HMP. The selection of appropriate constituents to serve as the basis for the assay will depend on the particular active substance. In exceptional cases it may be acceptable to replace the assay by other tests (e.g. bitterness value and swelling index) or other approaches (see Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products, EMEA/HMPC/CHMP/CVMP/214869/2006).

3.7. Reference standards

Reference standards (reference materials) are used for identity and purity testing and for content assignment and they play an essential role when ensuring and demonstrating adequate and consistent quality of herbal substances, herbal preparations and HMPs.

The reference standards may be a botanical sample of the herbal substance or a sample of the herbal preparation (e.g. extract or tincture) or a chemically defined substance, e.g. a constituent with known therapeutic activity, an active marker, an analytical marker or a known impurity.

Reference standards should meet quality standards appropriate for their intended use.

In the Ph. Eur. monographs on herbal substances and herbal preparations, pharmacopoeial reference standards are described for a dedicated purpose and they are only demonstrated to be suitable for the use indicated.

Where pharmacopoeial reference standards are available they should be used as primary standards. In cases where pharmacopoeial reference standards are not available, non-pharmacopoeial reference standards should be established. Their establishment should follow the guidance given in the Ph. Eur. chapter 5.12. "reference standards".

Herbarium samples

If the herbal substance is not described in the Ph. Eur. or in another Pharmacopoeia referred to in Annex I of Directive 2001/83/EC or in Annex II of Regulation (EU) 2019/6, as amended , a herbarium sample of the whole plant or part of the plant, if the whole plant is a tree, etc., should be available.

4. Specifications: Definition and justification

4.1. Definition of a specification

A specification is defined as a list of tests, references to analytical or biological 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 substance, herbal preparation or HMP should conform to be considered acceptable for its intended use. "Conformance to specification" means that the herbal substance/preparation 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.

4.2. Justification of a specification

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included.

The setting of a specification for a herbal substance/preparation and HMP is part of an overall control strategy. The justification should refer to pharmacopoeial standards, the control of raw materials and excipients, relevant development data, in-process testing, process evaluation/validation, analytical validation, stability testing. A reasonable range of expected analytical and manufacturing variability should be considered. Acceptance criteria should be based on data obtained from batches used to demonstrate manufacturing consistency.

Linking a specification to a manufacturing process is important, especially with regard to phytochemical profile and potential impurities and contaminants.

If multiple manufacturing sites are planned, it may be valuable to consider data from these sites in establishing the initial tests and acceptance criteria. If data from a single representative manufacturing site are used in setting tests and acceptance criteria, products manufactured at all sites should still comply with these criteria.

When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since the specification is chosen to confirm the quality rather than to characterise the product, the applicant should provide the rationale and justification for including and/or excluding testing for specific quality attributes.

Specifications for herbal substances are linked to:

- Botanical characteristics of the plant (binomial scientific name: genus, species, variety and author, chemotype, where applicable; usage of genetically modified organisms), part of the plant, its state (e.g. whole, fragmented, fresh, dry)
- Macroscopical and microscopical characteristics of the plant part
- Phytochemical characteristics: constituents with known therapeutic activity or active or analytical markers, toxic constituents (identity, assay, limit tests)
- Biological/geographical variation
- Cultivation/harvesting/drying conditions (microbial levels, mycotoxins (aflatoxins, ochratoxin A), heavy metals, pyrrolizidine alkaloids (PAs), polycyclic aromatic hydrocarbons (PAHs) etc.
- Pre-/post-harvest chemical treatments (pesticides, fumigants)
- Profile and stability of the constituents

Specifications for herbal preparations are linked to:

- Quality of the herbal substance (as above)
- Definition of the herbal preparation (genuine (native) drug extract ratio (DERgenuine), extraction solvent(s))
- Method of preparation from the herbal substance
- Microscopical characteristics (comminuted and powdered herbal substances as herbal preparation)
- Phytochemical characteristics of the herbal preparation: constituents with known therapeutic activity or active or analytical markers, toxic constituents (identification, quantitative determination, limit tests)
- Contaminants (pesticide residues, fumigants, mycotoxins (aflatoxins, ochratoxin A), heavy metals, pyrrolizidine alkaloids (PAs), and, if applicable, polycyclic aromatic hydrocarbons (PAHs) etc.)
- Drying conditions (e.g. microbial levels, residual solvents in extracts)
- Profile and stability of the constituents
- Microbial purity on storage
- Batches used in pre-clinical/clinical testing (safety and efficacy considerations)

Specifications for HMPs are linked to:

- The herbal substance and/or herbal preparation (as above)
- Manufacturing process (temperature effects, residual solvents)
- Pharmaceutical form (e.g. tablets, capsules, oral liquids)

- Profile and stability of the active substance/formulation in the packaging
- Excipients (e.g. antimicrobial preservatives, antioxidants)
- Microbial purity on storage
- Batches used in pre-clinical/clinical testing (safety and efficacy considerations)

It is the responsibility of the applicant to justify at which stage testing of impurities takes place.

The final posology of the HMP should be taken into account in controls to be applied on, when necessary, e.g. for PAs. Due to the inherent complexity of HMPs, there may be no single stability-indicating assay or parameter that profiles the stability characteristics. Consequently, the applicant should propose a series of product-specific, stability-indicating tests (e.g. chromatographic fingerprint tests), the results of which will provimpuriide assurance that changes in the quality of the product during its shelf-life will be detected. The determination of which tests should be included will be product-specific. Applicants are referred to the "Note for guidance on stability testing of new drug substances and products" (CPMP/ICH/2736/99 as revised), the "Guideline on stability testing of new veterinary drug substances and medicinal products" (CVMP/VICH/899/99 as revised) and 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).

5. Universal tests and acceptance criteria

Implementation of the recommendations in the following section should take into account "Note for guidance on validation of analytical procedures: Text and methodology" (CPMP/ICH/381/95) (or the corresponding VICH guidelines, CVMP/VICH/590/98 and CVMP/VICH/591/98).

5.1. Herbal substances

Herbal substances are a diverse range of botanical materials including leaves, herbs, roots, flowers, seeds, bark etc. A comprehensive specification should be developed for each herbal substance. 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 a monograph for a herbal substance exists in the Ph. Eur. or in 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 should be in accordance with this monograph. For non-pharmacopeial herbal substances the specification should be established on the basis of recent scientific data and should be set out in the same way as Ph. Eur. monographs. If the herbal substance is of fresh material, requirements according to the general monograph "Herbal Drugs" of Ph. Eur. should be taken into account.

The following tests and acceptance criteria are considered generally applicable to all herbal substances. The general monograph "Herbal Drugs" of Ph. Eur. should be consulted for their interpretation.

a) Definition:

A qualitative statement of the botanical source, the binomial scientific name, plant part used and its state (e.g. whole, fragmented, fresh, dry).

b) Characters:

A qualitative statement about the organoleptic character(s), the characteristic macroscopic and microscopic botanical characters of the herbal substance.

c) Identification:

Identification testing optimally should be able to discriminate between related species and/or potential adulterants/substitutes, which are likely to be present. Identification tests should be specific for the herbal substance and are usually a combination of three or more of the following:

Macroscopical characters, microscopical characters, chromatographic fingerprinting procedures, chemical reactions.

For the herbal substance, a characteristic fingerprint chromatogram should be established. The fingerprint is used for identity testing of the herbal substance. It can also be used to detect adulteration with other herbal substances.

d) Tests:

- Foreign matter
- Total ash
- Ash insoluble in hydrochloric acid[7]
- Water soluble extractive[7]
- Extractable matter[7]
- Water content

This test is important when the herbal substances are known to be hygroscopic. Acceptance criteria should be based on the limit given in the corresponding pharmacopoeial monograph. In case no monograph exists, limits for comparable herbal drugs should be taken into account. In case these limits cannot be met, individual limits may be justified by data on the effects of moisture absorption. A loss on drying procedure may be adequate; however, in some cases (essential-oil containing plants) an analytical procedure that is specific for water is required.

- Contaminants

Potential contaminants should be considered, and controls introduced, as appropriate. Acceptance criteria and suitable validated procedures should be used to control potential contaminants/residues. The analytical procedure and validation data should be provided considering the respective plant matrix.

In the case of use of fresh herbal substances (e.g. to produce expressed juices, fatty or essential oils) testing for contamination of the herbal substance can be omitted, where fully justified, and should be performed on the herbal preparation, where appropriate. The limits for the herbal substance can be transferred accordingly.

Periodic/Skip testing of contaminant residues may be acceptable where justified (see chapter 3.2). Justification should consider the plant material and conditions of cultivation/production, possible contamination from neighbouring farms, geographical origin (= region), and should be supported by a detailed risk assessment and data from different batches. The number of batches required to justify skip testing depends on the proposed testing interval and the level of impurities. Longer intervals require more batches. The data presented should preferably be from testing of consecutive batches.

[7] These tests might not apply to all herbal substances and should be justified by the applicant.

- Pesticide and Fumigant residues

The potential for residues of pesticides and fumigant agents should be considered.

For pesticide residues, the acceptance criteria of the Ph. Eur. (2.8.13.) or the acceptance criteria of Regulation (EC) 396/2005 should be applied, unless otherwise justified.
Where necessary, according to Ph. Eur. general chapter "pesticide residues" (2.8.13.), suitable validated methods should be used.

Regarding possible fumigant residues, confirmation by the supplier that fumigation of the herbal substance is not performed, is generally considered sufficient.
However, it should be taken into account that fumigation of commodities is often required by quarantine or export/import regulations. Therefore, the herbal substance should be tested for fumigants if no information is provided by the supplier. Where a fumigant is known to be non-persistent and this is supported by appropriate batch data, reduced testing may be acceptable.

- Heavy metals and other toxic elements

The acceptance criteria described in the general monograph "Herbal Drugs" of the Ph. Eur. should be applied, unless otherwise justified. For other metals not listed in this monograph, acceptance criteria should be based on safety considerations.

Where justified, herbal substances used for the production of extracts may exceed the limits for heavy metals specified in the monograph "Herbal Drugs" provided that the resulting extract satisfies these requirements. The need for inclusion of additional tests and acceptance criteria for other toxic elements (e.g. arsenic) should be investigated during development using a risk assessment approach. It should be noted that in some Ph. Eur. monographs limits for specific heavy metals/toxic elements are included. Additionally, the origin of the plant (cultivation or wild collection, region) and the plant specific ability to accumulate heavy metals/toxic elements should be taken into account.

The analytical procedures should be performed according to Ph. Eur. (2.4.27.).

- Microbial limits

For herbal substances, limits for microbial quality are not specified in the Ph. Eur. general chapters 5.1.4 "Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use" and 5.1.8 "microbiological quality of herbal medicinal products for oral use and extracts used in their preparation".

However, routine testing is generally required because the microbial purity is linked to production and storage and to mycotoxin contamination (GACP). Acceptance criteria should be established. Limits in Ph. Eur. under 5.1.8.A may be considered acceptable for herbal substances as starting material. Higher microbial limits may be acceptable and should be justified in relation to the specific herbal substance, GACP concept and subsequent processing. Reduction of the microbial count at the level of the herbal substance (e.g. source, appropriate harvest/collection and drying procedures, treatment with water vapour), herbal preparation (processing) and/or HMP (boiling water) should be taken into account when setting the limits.

The source of the herbal material should be taken into account when considering the inclusion of other possible pathogens (e.g. *Campylobacter* and *Listeria* species) in addition to those specified in the Ph. Eur.

Microbial counts should be determined using pharmacopoeial procedures (2.6.12., 2.6.31.) or other comparable, validated procedures.

- Mycotoxins (aflatoxins, ochratoxin A)

The potential for mycotoxin contamination should be considered.

For aflatoxins, the acceptance criteria and analytical procedure are described in Ph. Eur. 2.8.18. This method has been shown to be suitable for devil's claw root, ginger and senna pods. Its suitability for other herbal substances should be demonstrated or another validated method used.

For ochratoxin A, the analytical procedure and acceptance criteria are described in Ph. Eur. 2.8.22. This method has been shown to be suitable for liquorice extract and liquorice root. Its suitability for other herbal substances should be demonstrated or another validated method used. In cases where ochratoxin A contamination is relevant, the acceptance criteria given in the Ph. Eur. monograph for "Liquorice root" could also be acceptable for other herbal substances. Limits must be justified by the applicant and should consider the posology and patient group and take into account generally acceptable safety limits.

- Impurities from extraneous sources

The potential for impurities from extraneous sources should be considered.

Potentially toxic compounds arising from extraneous sources include, for example, pyrrolizidine alkaloids (PAs) from PA-containing weeds and polycyclic aromatic hydrocarbons (PAHs). It has been shown that PA-containing weeds can contaminate herbal substances used for the production of HMPs. PAH contamination of herbal substances can arise from environmental sources or specific conditions of processing of herbal substances. Suitable validated methods should be used and acceptance criteria justified. It is the responsibility of the applicant to establish at which stage testing for such impurities takes place. In order to ensure that the levels of PAs do not exceed the daily intake recommended for HMPs, it is anticipated that in most cases testing the herbal preparation will ensure a more homogeneous matrix than testing the herbal substance. With regard to the control and limits for PAs, guidance by the Committee on Herbal Medicinal Products (EMA/HMPC/893108/2011 Rev. 1) should be taken into account.

- Radioactivity

Radioactive contamination should be tested for, if there are reasons for concern.

- Degradation products

Where relevant, appropriate limits should be proposed for potentially toxic degradants formed on storage or those that might arise as a result of decontamination treatments. Possible degradation products arising from irradiation of the herbal substance, should also be considered where such treatment is used.

- Toxic constituents

In the case of potentially toxic constituents, e.g. ascaridole, thujone, pulegone, menthofuran, quantitative determination of their content with details of the validated analytical procedure may be required. If relevant, information on their potential toxicity (either by reference to the literature or by presentation of data) should be given to justify the proposed limits.

- Other appropriate tests (e.g. swelling index)

e) Assay:

In the case of herbal substances with constituents of known therapeutic activity or with active markers, assays of their content are required with details of the analytical procedure. Where possible, a specific, stability-indicating procedure should be chosen. In cases where use of a non-specific assay is justified, other supporting analytical procedures may be used to achieve overall specificity, if required.

In the case of herbal substances where the constituents responsible for the therapeutic activity or active markers are unknown, assays of analytical markers or other justified determinations (see 3.6) are required. The appropriateness of the choice of markers should be justified (see 3.1.3).

5.2. Herbal preparations

Herbal preparations are also diverse in character ranging, according to Ph. Eur., from simple, comminuted (powdered or cut) plant material to extracts, tinctures, essential oils, expressed juices and processed exudates. A comprehensive specification should be developed for each herbal preparation based on recent scientific data. If a monograph for a herbal preparation exists in the Ph. Eur. or in 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 should be in accordance with this monograph, taking into account the provisions of Ph. Eur. 5.23. monographs on herbal drug extracts (information chapter). For non-pharmacopeial herbal preparations the specification should be established on the basis of recent scientific data and should be set out in the same way as Ph. Eur. monographs. The general monographs "Herbal Drug Preparations", "Herbal Drug Extracts" and "Essential Oils" of the Ph. Eur. should be consulted for the interpretation of the following requirements.

The following tests and acceptance criteria are considered generally applicable to all herbal preparations.

a) Definition:

A statement of the botanical source, and the type of preparation (e.g. dry or liquid extract). For extracts, the extraction solvent as well as the ratio between the quantity of herbal substance used in the manufacture of the extract, and the quantity of genuine (native) herbal extract obtained (DERgenuine) must be stated. Information on excipients included in the final extract should also be specified.

b) Characters:

A qualitative statement about the organoleptic characters of the herbal preparation, where characteristic.

c) Identification:

Identification tests should be specific for the herbal preparation and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur. Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS may be acceptable.

Chromatographic fingerprinting: For the herbal preparation, a characteristic fingerprint chromatogram should be established by means of qualitative analysis. The parameter should be tested at release and during stability studies. During stability/retest testing the fingerprint chromatogram should remain comparable to the fingerprint at the initial time point value to demonstrate consistent quality.

d) Tests:

- Water content

The acceptance criteria may be justified with data on the effects of hydration or moisture absorption. A Loss on drying procedure may be adequate; however, in some cases (essential oil containing preparations) an analytical procedure that is specific for water is required. Where applicable, acceptance criteria should be based on requirements given in the monograph "Herbal Drugs" and "Herbal Drug Extracts" in Ph. Eur.

- Particle size

To be considered for cut or powdered herbal substances intended for use in herbal teas or solid dosage forms of HMPs and also for extracts for use in HMPs.

Particle size can have a significant effect on disintegration time, dissolution rate, bioavailability, and/or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.

- Impurities

Residual solvents in dry or soft extracts arising from the extraction process:

Refer to the Ph. Eur. general text on residual solvents (5.4) for detailed information (or VICH GL18 on residual solvents) and Ph. Eur. monograph "Herbal Drug Extracts" (0765).

Pesticides, fumigants, mycotoxins and heavy metal/toxic element residues:

In accordance with the Ph. Eur. monograph "Herbal Drugs" (1433), routine testing or periodic testing, in some cases, is required for pesticides, fumigants, mycotoxins (aflatoxins, ochratoxin A) and heavy metals. Therefore, justification should be provided that the contaminants do not accumulate during the manufacturing process. Testing of these contaminants in the herbal preparation is usually considered not necessary if tested on the herbal substance. Particular attention should be paid to pesticide residues and mycotoxins that are soluble in lipophilic solvents and so can be concentrated in herbal preparations prepared with lipophilic extraction solvents.

In the situation where fresh herbal substances are used, according to the Ph. Eur. monograph "Herbal Drug Extracts" (0765), testing of contaminants in herbal preparations may be necessary.

If testing for contaminants is necessary in the herbal preparation, the limits for the herbal substance according to the Ph. Eur. are applicable.

Where justified, processing factors/correction factors may be included in the calculation (e.g. for pesticide residues).

- Microbial limits

Acceptance criteria for the microbiological quality of herbal preparations intended for oral use should be in-line with Ph. Eur. chapter 5.1.8. The microbiological quality of herbal preparations to be administered by routes other than oral use should correspond to the acceptance criteria for the intended route of administration according to Ph. Eur. chapter 5.1.4.

Microbial counts should be determined using pharmacopoeial procedures (2.6.12, 2.6.31) or other validated procedures.

- Toxic constituents

In the case of potentially toxic constituents, e.g. ascaridole, thujone, pulegone, menthofuran, quantitative determination of their content with details of the validated analytical procedure are

required. If relevant, information on their potential toxicity (either by reference to the literature or by presentation of data) should be given to justify the proposed limits.

- Degradation products

Where relevant, appropriate limits should be proposed for potentially toxic degradants formed during processing or on storage.

- Impurities from extraneous sources

Potentially toxic compounds arising from extraneous sources include, PAs and PAHs (see 5.1). It is the responsibility of the applicant to establish at which stage testing for such impurities takes place. To ensure that the limits for PAs do not exceed the daily intake recommended for HMPs it is anticipated that in most cases testing the herbal preparation will ensure a more homogeneous matrix than testing the herbal substance. With regard to the control and limits for PAs, the requirements of the Committee on Herbal Medicinal Products (HMPC: Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids (EMA/HMPC/328782/2016)) should be taken into account.

e) Assay:

In the case of herbal preparations with constituents of known therapeutic activity or with active markers, assays of their content are required with details of the analytical procedure and validation data. Where possible, a specific, stability-indicating procedure should be chosen. In cases where use of a non-specific assay is justified, other supporting analytical procedures may be used to achieve overall specificity, if required. For example, where a UV/visible spectrophotometric assay is used for hydroxyanthracene glycosides, a combination of the assay and a suitable test for identification (e.g. fingerprint chromatography) can be used.

In the case of herbal preparations where constituents of known therapeutic activity or active markers are not known, assays of analytical markers or other justified determinations are required. The appropriateness of 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.

5.3. Vitamins and minerals in traditional herbal medicinal products for human use

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.

The following tests and acceptance criteria are considered generally applicable to vitamins/minerals in THMPs for human use:

a) Identification:

Identification tests should establish the specific identity of the vitamin(s) and/or mineral(s).

b) Assays:

Validated assays of vitamins and minerals are required.

c) Impurities:

Refer to the ICH "Note for guidance on impurities in new drug products" (CPMP/ICH/2738/99) and Ph. Eur. general text on "residual solvents" (5.4.) for detailed information.

Impurities arising from degradation of the vitamin(s) should be monitored in the THMPs for human use. When it has been demonstrated conclusively by provision of a significant body of data, generated using appropriate analytical methods, that the vitamin(s) do not degrade in the specific formulation and under the specific storage conditions proposed in the application, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

5.4. Herbal medicinal products

The following tests and acceptance criteria are considered generally applicable to all HMPs:

a) Description:

A qualitative description of the dosage form should be provided (e.g. size, shape, colour). The acceptance criteria should include the final acceptable appearance at the end of the shelf-life. If colour changes occur during storage, a quantitative procedure may be appropriate.

b) Identification:

Identification tests should establish the specific identity of the herbal substance(s) and/or herbal preparation(s), in the HMP and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur. Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS may be acceptable. In the case of HMPs containing comminuted (powdered or cut) herbal substances, microscopical and macroscopical characterisation could be used for identification in combination with other methods, if justified.

c) Chromatographic fingerprinting:

A characteristic fingerprint chromatogram should be established and justified taking account of the fingerprints for the active substance(s). With regard to combination products, the principles set out in Guideline EMA/HMPC/CHMP/CVMP/287539/2005 as revised should be applied. For this purpose, chromatograms from identification or assay test methods can often be used as a basis for chromatographic fingerprinting. The parameter should be tested at release and during stability studies. In the shelf-life specification, the acceptance criteria should specify that the fingerprint chromatogram is comparable to the initial fingerprint obtained at release.

d) Impurities:

Refer to the ICH/VICH "Note for guidance on impurities in new drug products"/"Guideline on impurities in new veterinary medicinal products" (CPMP/ICH/2738/99 and CVMP/VICH/838/99 as revised) and the Ph. Eur. general text on "residual solvents" (5.4.) for detailed information.

Impurities arising from the herbal substance(s) and/or herbal preparations, e.g. contaminants such as pesticide/fumigant residues, heavy metals, mycotoxins, PAs, PAHs: If controlled during the testing of the herbal substance/preparation, it is not necessary to test for these in the HMP.

Similarly, *residual solvents arising from the manufacture of the herbal preparation* (e.g. an extract) do not need to be controlled in the HMP, provided they are appropriately controlled in the extract specification. However, solvents used, for example in tablet coating, will need to be controlled in the HMP.

In cases where potentially *toxic degradation products* of the herbal substance/preparation are evident (e.g. aglycones from hydroxyanthracene glycosides), they should be monitored in the HMP and acceptance limits should be stated for such degradation products.

e) Toxic constituents:

In the case of potentially toxic constituents, e.g. ascaridole, thujone, pulegone, menthofuran, quantitative determination of their content with details of the validated analytical procedure are required. If relevant, information on their potential toxicity (either by reference to the literature or by presentation of data) should be given to justify the proposed limits.

f) Microbial limits:

Acceptance criteria for the microbiological quality of HMPs intended for oral use should be in-line with Ph. Eur. chapter 5.1.8. The microbiological quality of HMPs to be administered by routes other than oral use should correspond to the acceptance criteria for the intended route of administration according to Ph. Eur. chapter 5.1.4.

Microbial counts should be determined using pharmacopoeial procedures (2.6.12., 2.6.31.) or other validated procedures.

Skip testing for microbial contamination may be acceptable for some HMPs, if justified according to the Guideline on specifications: test procedures and acceptance criteria for new drug substances and new drug products-Chemical substances, decision tree 8: Microbiological attributes of non-sterile drug products (CPMP/ICH/367/96 and EMEA/CVMP/VICH/810/04).

g) Assay:

In the case of products containing herbal substances and/or herbal preparations with constituents of known therapeutic activity, validated assays of the content of these constituents are required along with details of the analytical procedure(s). Where appropriate, a specific, stability-indicating procedure should be chosen. In cases where the use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where a UV/visible spectrophotometric assay is used e.g. with hydroxyanthracene glycosides, a combination of the assay and a suitable test for identification (e.g chromatographic fingerprinting) can be used.

In the case of HMPs containing herbal substance(s) and/or herbal preparation(s) where the constituents with known therapeutic activity are not known, validated assays of active or analytical markers or other justified determinations are required, as described above. In cases where use of a non-specific assay is justified, other supporting analytical procedures may be used to achieve overall specificity. In cases where a specific assay of each active substance of a HMP is not possible, other justified determinations are required (see "Guideline on quality on combination of herbal medicinal products/traditional herbal medicinal products" (EMEA/HMPC/CHMP/CVMP/214869/2006)).

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

h) Vitamins and/or minerals:

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

6. Specific tests and acceptance criteria for herbal medicinal products

In addition to the universal tests listed above, the following provides examples of tests which may be considered applicable to HMPs on a case-by-case basis (see also Ph. Eur. General Monographs on dosage forms). Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the HMP for batch control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

Additional tests and acceptance criteria generally should be included for particular HMPs. The following selection presents a representative sample of both the HMPs and the types of tests and acceptance criteria, which may be appropriate. The specific dosage forms addressed include solid oral HMPs, and liquid HMPs. Application of the concepts in this guideline to other dosage forms is encouraged.

6.1. Tablets (coated and uncoated) and hard capsules

One or more of these tests may also be applicable to soft capsules and granules.

a) Dissolution/disintegration:

In the case of immediate release HMPs for which constituents with therapeutic activity are not known, the test for *in vitro* active substance release can be omitted.

For immediate release products containing herbal preparations, which are highly soluble throughout the physiological pH range, disintegration testing may sometimes be sufficient. Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases, dissolution testing may not always be necessary, or may be proposed as a periodic test. It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.

Single-point measurements are normally considered to be suitable for immediate-release dosage forms. For modified-release dosage forms, appropriate test conditions and sampling procedures should be established. For example, multiple-time-point sampling should be performed for extended-release dosage forms, and two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms. In these cases, it is important to consider the populations of individuals or target animal species who will be taking the HMP (e.g. achlorhydric, elderly) when designing the tests and acceptance criteria.

Where multiple-point acceptance criteria are necessary, *in vitro/in vivo* correlation may be used to establish these criteria when human or target animal species bioavailability data are available for formulations exhibiting different release rates. Where such data are not available, and drug release cannot be shown to be independent of *in vitro* test conditions, then acceptance criteria should be established on the basis of available batch data. Normally, the permitted variability in release rate at any given time point should not exceed a total numerical difference of ± 10% of the labelled content of herbal substance or herbal preparation (i.e. a total variability of 20%: a requirement of 50% ± 10% thus means an acceptable range from 40% to 60%), unless a wider range is justified.

b) Hardness/friability:

It is normally appropriate to perform hardness and/or friability testing as an in-process control. Under these circumstances, it is normally not necessary to include these attributes in the specification. If the

characteristics of hardness and friability have a critical impact on HMP quality (e.g. chewable tablets), acceptance criteria should be included in the specification.

c) Uniformity of mass:

The pharmacopoeial procedure should be used (Ph. Eur. 2.9.5.). If appropriate, this test may be performed as in-process control; the acceptance criteria should be included in the specification.

d) Water content:

A test for water content should be included when appropriate. The acceptance criterion may be justified with data on the effects of or water absorption on the HMP. In some cases, a Loss on drying procedure may be adequate; however, in certain cases (e.g. essential oil containing preparations), a more specific procedure (e.g. Karl Fischer titration) is required.

6.2. Oral liquids

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids. Likewise, one or more of the following specific tests will normally be applicable to liquid preparations intended for routes other than oral use (see 6.3. Oromucosal preparations).

a) Uniformity of mass:

Generally, acceptance criteria should be set for weight variation, fill volume, and/or uniformity of fill. Pharmacopoeial procedures should be used.

If appropriate, tests may be performed as in-process controls; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of drug, divided by the total number of doses expected. If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

b) pH - value:

Acceptance criteria for pH should be provided where applicable and the proposed range justified.

d) Antimicrobial preservative content:

For oral liquids needing an antimicrobial preservative, acceptance criteria for identification and assay of the preservative content should be included in the specification. These criteria should be based on the levels necessary to maintain microbiological product quality throughout the shelf-life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using the Ph. Eur. antimicrobial preservative effectiveness test.

Release testing for antimicrobial preservative content should normally be performed. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scale-up, and at the end of shelf-life (e.g. in stability testing: see the "Guideline on stability testing of existing active substances and related finished products" (CPMP/QWP/122/02 and EMEA/CVMP/846/99 as revised); "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), although chemical testing for preservative content is the attribute normally included in the specification.

e) Antioxidant preservative content:

Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

f) Extractables and leachables:

Generally, where development and stability data show no significant evidence of extractables/leachables from the container/closure system, elimination of this test may be proposed. This should be reinvestigated if the container/closure system changes.

Where data demonstrate the need, tests and acceptance criteria for extractables/leachables from the container-closure system components (e.g. rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in non-glass systems or in glass containers with non-glass closures. The container-closure components should be listed, and data collected for these components as early in the development process, as possible.

g) Ethanol content:

Where it is declared quantitatively on the label in accordance with pertinent regulations, the ethanol content should be tested and specified.

h) Dissolution:

In addition to the attributes recommended immediately above, it may be appropriate (e.g. where constituents of the herbal substance or herbal preparation are sparingly soluble) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated.

Single-point measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms. Acceptance criteria should be set based on the observed range of variation and should take into account the dissolution profiles of the batches that showed acceptable performance *in vivo*. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Dissolution testing may be performed as an in-process test, or as a release test, depending on its relevance to product performance. The discussion of dissolution for solid oral dosage forms (above), and of particle size distribution (immediately following), should also be considered here.

i) Particle size distribution:

Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations.

Particle size distribution testing may be performed as an in-process test or as a release test, depending on its relevance to product performance. If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper and/or lower particle size limits should be well defined.

Acceptance criteria should be set, based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance *in vivo*, as well as, the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

j) Redispersibility:

For oral suspensions, which settle on storage (produce sediment) acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate test. The procedure (mechanical or manual) should be indicated. Time required to achieve re-suspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip testing, or elimination of this attribute from the specification.

k) Rheological properties:

For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity) in the specification. The test and acceptance criteria should be stated. Data generated during product development may be sufficient to justify skip testing, or elimination of this attribute from the specification.

l) Specific gravity:

For oral suspensions, or relatively viscous or non-aqueous solutions, acceptance criteria for specific gravity may be appropriate. Testing may be performed as an in-process control.

m) Reconstitution time:

Acceptance criteria for reconstitution time should be provided for dry powder products, which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip testing or elimination of this attribute from the specification.

n) Water content:

For oral products requiring reconstitution, a test and an acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterised during the development of the product. In certain cases (e.g. essential oil containing preparations), a more specific procedure (e.g. Karl Fischer titration) is required.

6.3. Oromucosal preparations

In accordance with Ph. Eur., oromucosal preparations are solid, semi-solid or liquid preparations, containing one or more active substances intended for administration to the oral cavity and/or the throat to obtain a local or systemic effect. For many oromucosal preparations, it is likely that some proportion of the active substance(s) will be swallowed and may be absorbed via the gastrointestinal tract.

Oromucosal preparations may contain suitable antimicrobial preservatives and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilising, stabilising, flavouring and sweetening agents. Solid preparations may in addition contain glidants, lubricants and excipients capable of modifying the release of the active substance(s).

Several categories of preparations for oromucosal use may be distinguished:

gargles; mouthwashes; gingival solutions; oromucosal solutions and oromucosal suspensions; semi-solid oromucosal preparations (including for example gingival gel, gingival paste, oromucosal gel, oromucosal paste); oromucosal drops, oromucosal sprays and sublingual sprays (including oropharyngeal sprays); lozenges and pastilles; compressed lozenges; sublingual tablets and buccal tablets; oromucosal capsules; mucoadhesive preparations; orodispersible films.

6.4. Herbal medicinal products containing exclusively herbal substances (e.g. herbal teas)

In addition to the universal tests one or more of these tests may be applicable to HMPs containing exclusively herbal substances.

a) Loss on drying:

To be specified depending on the plant parts present in the HMP, if not performed on the herbal substance.

b) Uniformity of mass/Average mass of the sachet (e.g. herbal tea):

Generally, acceptance criteria should be set for weight variation and/or fill volume. Pharmacopoeial procedures should be used (Ph. Eur. "Herbal teas" and "Herbal teas, instant"). If appropriate, tests may be performed as in-process controls; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multi-dose products.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of herbal substance, divided by the total number of doses expected. If dispensing equipment is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

c) Assay:

In the case of such HMPs containing herbal substances with constituents of known therapeutic activity, validated assays for these constituents are required along with details of the analytical procedure(s). Where appropriate, a specific, stability-indicating procedure should be chosen. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. (e.g. a UV/visible spectrophotometric assay for anthraquinone glycosides in combination with fingerprint chromatography for identification). In the case of products containing herbal

substance(s) where the constituents with known therapeutic activity are not known, assays of active or analytical markers or other justified determinations are required. The choice of such markers should be justified.

For HMPs consisting of one herbal substance without any excipients, the assay can be carried out on the herbal substance, if justified.

Finally, in cases of multi-component HMPs where an assay of each herbal substance is not possible, the applicant should justify how reproducibility of the finished product is guaranteed and tested ("Guideline on quality on combination of herbal medicinal products/traditional herbal medicinal products" (EMEA/HMPC/CHMP/CVMP/214869/2006)).

d) Particle size:

Suitable acceptance criteria should be given by the manufacturer.

7. 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.

Degradation product: Any impurity resulting from a chemical change in the composition of the active substance brought about during manufacture and/or storage of the active substance/medicinal product by the effect of, e.g. light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system. Due to the particular nature of herbals, for herbal substances/herbal preparations/HMPs, in general, only toxicologically relevant degradation products should be specified.

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

- **Genuine (Native) drug extract ratio (DERgenuine):** 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 (DERtotal):** is the ratio between the quantity of herbal drug (herbal substance) used in the manufacture of an extract and the quantity of whole extract

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 the European Pharmacopoeia, 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. 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.

Impurity: (1) Any component of the herbal substance, which is not the entity defined as the herbal substance. (2) Any component of the herbal preparation/herbal medicinal product that is not the entity defined as the herbal substance/preparation or an excipient in the herbal preparation/herbal medicinal product.

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 or pharmacological 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 extract).

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 and biological 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 substance/preparation or HMP should conform to be considered acceptable for its intended use. "Conformance to specification" means that the herbal

substance/preparation 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/registration holder and approved by regulatory authorities.

Specific test: A test, which is considered to be applicable to a particular herbal substance/preparation or a particular HMP depending on their specific properties and/or intended use.

Standardisation: means adjusting the herbal substance/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): are 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.

Unidentified impurity: An impurity, which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

Universal test: A test, which is considered to be potentially applicable to all herbal substances/preparations, or all herbal medicinal products; e.g. appearance, identification, assay and impurity tests.

8. 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

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/214869/2006)

Guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/201116/2005 as revised)

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)

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

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

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

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

Note for guidance on impurities in new drug products (CPMP/ICH/2738/99)

Guideline on impurities in new veterinary medicinal products (CVMP/VICH/838/99 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)

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 stability testing: stability testing of new drug substances and products (CPMP/ICH/2736/99 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)

Ph. Eur. general chapter on microbiological quality of herbal medicinal products for oral use and extracts used in their preparation (5.1.8.)

Ph. Eur. general chapter on reference standards (5.12.)

Ph. Eur. general chapter on pesticide residues (2.8.13.)

Ph. Eur. general text on residual solvents (5.4.)

VICH GL18 on residual solvents (EMA/CVMP/VICH/502/99)

Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids (EMA/HMPC/328782/2016)

Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs), including recommendations regarding contamination of herbal medicinal products with PAs (EMA/HMPC/893108/2011 Rev. 1)

Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/41500/2010 Rev. 5)

Reflection paper on the use 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)

Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin