



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 March 2011
EMA/CPMP/QWP/2820/00 Rev. 2
EMA/CVMP/815/00 Rev. 2
EMA/HMPC/162241/2005 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)
Committee on Herbal Medicinal Products (HMPC)

Guideline on specifications: test procedures and acceptance criteria for herbal substances¹, herbal preparations² and herbal medicinal products³/traditional herbal medicinal products

Final

Discussion at the HMPC	January – March 2005
Draft agreed by Quality Working Party	April 2005
Adoption by CHMP for release for consultation	26 May 2005
Adoption by CVMP for release for consultation	15 June 2005
End of consultation (deadline for comments)	15 September 2005
Discussion at the HMPC	November 2005 – January 2006
Adoption by the HMPC	22 January 2006
Agreed by Quality Working Party	February 2006
Adoption by CHMP	23 March 2006
Adoption by CVMP	16 March 2006
Date for coming into effect	1 October 2006
Revision by HMPC Quality Drafting Group	February 2011 April 2011

¹ The term "herbal substance" should be considered as equivalent to the term "herbal drug" as defined in the European Pharmacopoeia.

² The term "herbal preparation" should be considered as equivalent to the term "herbal drug preparation" as defined in the European Pharmacopoeia.

³ Throughout the guideline and unless otherwise specified, the term "herbal medicinal product" includes "traditional herbal medicinal product".



Adoption by the HMPC	31 March 2011
Adoption by CHMP	12 September 2011
Adoption by CVMP	14 September 2011

Explanatory note: This guideline updates the CPMP/CVMP/QWP 'Guideline on specifications: test procedures and acceptance criteria for herbal drugs, herbal drug 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 on the market will be affected by this guideline, with the exception of traditional herbal medicinal products 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' were introduced, which take into account new and revised guidelines, the European Pharmacopoeia revised general monograph 'Herbals Drugs', as well as new requirements for impurities. Given the nature of this update, a concept paper or public consultation was not required.

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Table of contents

1. Introduction	5
1.1. Objective of the guideline	5
1.2. Background	5
1.3. Scope of the guideline	6
2. General concepts	6
2.1. Characterisation	6
2.1.1. Macroscopical/microscopical characterisation	7
2.1.2. Phytochemical characterisation	7
2.1.3. Impurities	7
2.1.4. Biological variation	7
2.2. Design and development considerations	7
2.3. Pharmacopoeial tests and acceptance criteria	8
2.4. Periodic/skip testing	8
2.5. Release versus shelf-life acceptance criteria	8
2.6. In-process tests	8
2.7. Alternative procedures	8
2.8. Evolving technologies	9
2.9. Reference standard	9
2.10. Statistical concepts	9
3. Guidelines	9
3.1. Specifications: Definition and justification	9
3.1.1. Definition of specifications	9
3.1.2. Justification of specifications	10
3.2. Universal tests/criteria	11
3.2.1. Herbal substances	11
3.2.2. Herbal preparations	13
3.2.3. Vitamins and minerals in traditional herbal medicinal products for human use	15
3.2.4. Herbal medicinal products	15
3.3. Specific tests/criteria	16
3.3.1. Herbal medicinal products	17

4. Definitions 23

1. Introduction

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 to support applications for marketing authorisation or registration according to Directives 2001/82/EC and 2001/83/EC as amended. It should be read in conjunction with the 'Guideline on quality of herbal medicinal products' (EMA/CPMP/QWP/2819/00, EMA/CVMP/814/00, EMA/HMPC/201116/2005, as revised).

A simplified registration procedure was established for traditional herbal medicinal products for human use under Directive 2004/24/EC. The quality of a medicinal product is independent of its traditional use; therefore all general principles of quality also apply to traditional herbal medicinal products for human use. Traditional herbal medicinal products for human use may additionally contain vitamins 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, specifications 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 herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal substance/preparation or herbal medicinal product, 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 and approved by regulatory authorities.

Specifications are one part of a total control strategy for the herbal substance/preparation and herbal medicinal product 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)' (EMA/HMPC/246816/2005) and Good Manufacturing Practice (GMP), and a validated manufacturing process, e.g., raw material testing, in-process testing, stability testing, etc.

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

1.3. Scope of the guideline

The quality of herbal substances, herbal preparations and herbal medicinal products 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 and herbal medicinal products at release and during the shelf-life. Specifications are an important component of quality assurance, but are not its only component. All of the considerations listed above are necessary to ensure consistent production of herbal substances/preparations and herbal medicinal products of high quality.

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

Guidance is provided with regard to acceptance criteria, which should be established for all herbal substances/preparations and herbal medicinal products, i.e. universal 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.

2. 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.

2.1. Characterisation

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/preparation or herbal medicinal product (which includes a detailed evaluation of the botanical and phytochemical aspects of the plant, manufacture of the preparation and the herbal medicinal product) is therefore essential to allow specifications to be established, which are both comprehensive and relevant.

Acceptance criteria should primarily be established and justified based on information from batches used in pre-clinical/clinical studies or described in relevant bibliographic data. However, 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 may need to be taken into account, where available.

Extensive characterisation usually is performed only in the development phase and where necessary following significant process changes. If necessary, 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.

2.1.1. Macroscopical/microscopical characterisation

Includes features, which distinguish the herbal substance from potential adulterants and substitutes.

2.1.2. Phytochemical characterisation

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

2.1.3. Impurities

Impurities can be classified as follows:

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

In addition, for herbal medicinal products the following groups of impurities should be addressed, if appropriate:

Contaminants, which are impurities such as toxic metals, residues of pesticides and fumigants, mycotoxins (aflatoxins, ochratoxin A), as well as microbial contamination, including those arising from extraneous sources, and radioactive substances, if relevant.

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

Residual solvents, which are impurities arising from manufacturing processes.

2.1.4. Biological variation

Includes the use of historical batch data and published information concerning biological variation for justification of specification.

2.2. Design and development considerations

The experience and data accumulated during the development of a herbal substance/preparation or herbal medicinal product should form the basis for the setting of specifications. In general, it is only necessary to test the herbal medicinal product for quality attributes uniquely associated with the particular dosage form and the herbal substance or herbal preparation present. For example, it may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

- reduced testing for pesticide residues where a herbal substance is grown under strict organic cultivation without pesticides etc and potential contamination from adjacent plantations has been eliminated,

- excluding or reducing tests for microbial limits in herbal preparations such as extracts or tinctures depending on the ethanol content if justified by scientific evidence (Questions & answers (Q&A) on quality of herbal medicinal products/traditional herbal medicinal products EMA/HMPC/41500/2010).

2.3. Pharmacopoeial tests and acceptance criteria

The European Pharmacopoeia contains important requirements pertaining to certain analytical procedures and acceptance criteria that are relevant to herbal substances, herbal preparations and their herbal medicinal products. Wherever they are appropriate, pharmacopoeial methods should be utilised.

2.4. 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. This represents a less than full schedule of testing and should therefore be justified and presented to the regulatory authority prior to implementation. This concept may be applicable to, for example, dissolution, residual solvents, and microbiological testing, e.g., for solid oral dosage forms (Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, CPMP/ICH/367/96, and Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances, EMEA/CVMP/VICH/10/04). Therefore, this concept may sometimes be implemented post-approval in accordance with GMP, and approval by the Regulatory Authority.

2.5. Release versus shelf-life acceptance criteria

The concept of different acceptance criteria for release versus shelf-life specifications applies to herbal medicinal products. This concept can also apply in exceptional cases to herbal substances and herbal preparations, if justified. It pertains to the establishment of more restrictive criteria for the release of a herbal medicinal product than are applied to the shelf-life. Examples where this may be applicable include assay and impurity (degradation product) levels.

2.6. In-process tests

In-process tests are tests, which may be performed during the manufacture of either the herbal preparation or herbal medicinal product, rather than as part of the formal battery of tests, which are conducted prior to product release. In-process tests, 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.

2.7. Alternative procedures

Alternative procedures are those, which may be used to measure an attribute when such procedures control the quality of the herbal substance/preparation or herbal medicinal product to an extent, which is comparable or superior to the official procedure. Example: for tablets that have been shown not to

degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic. However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf-life of the product.

2.8. Evolving technologies

New analytical technology and modifications to existing technology are continuously being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justifiable.

2.9. Reference standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. In the case of herbal medicinal products, the reference standard may be a botanical sample of the herbal substance, 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 or an analytical marker or a known impurity. The reference standard has a quality appropriate to its use. The composition of reference standards of herbal substances and herbal preparations intended for use in assays should be adequately controlled and the purity of a standard should be measured by validated quantitative procedures.

- Herbarium samples

If the herbal substance is not described in the European Pharmacopoeia or in another Pharmacopoeia of a Member State, a herbarium sample of the whole plant or part of the plant, if the whole plant is a tree, etc., must be available.

2.10. Statistical concepts

Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.

3. Guidelines

3.1. Specifications: Definition and justification

3.1.1. Definition of specifications

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 and herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal substance/preparation and/or herbal medicinal product, 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 and approved by regulatory authorities.

It is possible that, in addition to release tests, a specification may list in-process tests, periodic (skip) tests, and other tests, which are not always conducted on a batch-by-batch basis. In such cases the applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency. In this situation, the herbal substance/preparation and/or herbal medicinal product should meet the acceptance criteria if tested.

It should be noted that changes in the specification after approval of the application will need prior approval by the regulatory authority.

3.1.2. Justification of specifications

The setting of specifications for a herbal substance/preparation and herbal medicinal product is part of an overall control strategy which includes control of raw materials and excipients, in-process testing, process evaluation/validation, stability testing and testing for consistency of batches. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterise the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. The following points should be taken into consideration when establishing scientifically justifiable specifications.

Specifications for herbal substances are linked to:

- botanical characteristics of the plant (genus, species, variety, chemotype; usage of genetically modified organisms), parts of the plants,
- macroscopical and microscopical characterisation, phytochemical characteristics of the plant part constituents with known therapeutic activity or markers, toxic constituents (identity, assay, limit tests),
- biological/geographical variation,
- cultivation/harvesting/drying conditions (microbial levels, mycotoxins (aflatoxins, ochratoxin A), toxic metals 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 (drug extract ratio, extraction solvent(s)),
- method of preparation from the herbal substance,
- constituents – constituents with known therapeutic activity or active or analytical markers,
- other constituents (identification, assay, limit tests),
- drying conditions (e.g. microbial levels, residual solvents in extracts),

Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products /traditional herbal medicinal products

EMA/CPMP/QWP/2820/00 Rev. 2

EMA/CVMP/815/00 Rev. 2

EMA/HMPC/162241/2005 Rev. 2

Committee for Medicinal Products for Human Use (CHMP)

Committee for Medicinal Products for Veterinary Use (CVMP)

Committee on Herbal Medicinal Products (HMPC)

- profile and stability of the constituents,
- microbial purity on storage,
- batches used in pre-clinical/clinical testing (safety and efficacy considerations).

Specifications for herbal medicinal products are linked to:

- quality of the herbal substance and/or herbal preparation,
- manufacturing process (temperature effects, residual solvents),
- profile and stability of the active substance/formulation in packaging,
- batches used in pre-clinical/clinical testing (safety and efficacy considerations).

Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially with regard to product-related substances, product-related impurities and process-related impurities.

Historical batch data should be taken into account where available.

Changes in the manufacturing process and degradation products produced during storage may result in a product, which differs from that used in pre-clinical and clinical development. The significance of these changes should be evaluated.

Due to the inherent complexity of herbal medicinal products 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, the results of which will provide 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/846/99 as revised).

3.2. Universal tests/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).

3.2.1. Herbal substances

Herbal substances are a diverse range of botanical materials including leaves, herbs, roots, flowers, seeds, bark etc. A comprehensive specification must be developed for each herbal substance even if the starting material for the manufacture of the herbal medicinal product is a herbal preparation. In the case of fatty or essential oils used as active substances of herbal medicinal products a specification for the herbal substance is required unless justified. The specification should be established on the basis of recent scientific data and should be set out in the same way as the European Pharmacopoeia

monographs. The general monograph 'Herbal Drugs' of the European Pharmacopoeia should be consulted for interpretation of the following requirements.

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

a) Definition: a qualitative statement of the botanical source, plant part used and its state (e.g. whole, reduced, powdered, fresh, dry). It is also important to know the geographical source(s) and the conditions under which the herbal substance is obtained.

b) Characters: a qualitative statement about the organoleptic character(s) where characteristic and the 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 procedures, Chemical reactions.

d) Tests:

Foreign matter.

Total ash.

Ash insoluble in hydrochloric acid⁴.

Water soluble extractive⁴.

Extractable matter⁴.

Particle size: For some herbal substances intended for use in herbal teas or solid herbal medicinal products, particle size can have a significant effect on dissolution rates, 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. Particle size can also affect the disintegration time of solid dosage forms.

Water content: This test is important when the herbal substances are known to be hygroscopic. For non-pharmacopoeial herbal substances, acceptance criteria should 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); a detection procedure that is specific for water is required.

Contaminants:

– Inorganic impurities, toxic (heavy) metals: The need for inclusion of tests and acceptance criteria for inorganic impurities should be studied during development and based on knowledge of the plant species, whether it is wild or cultivated and the manufacturing process. Acceptance criteria will ultimately depend on safety considerations. Where justified, procedures and acceptance criteria for Sulphated ash/Residue on ignition/Heavy metals (2.4.27) should follow pharmacopoeial precedents.

– Microbial limits: There may be a need to specify the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria. The source of the herbal material should be taken into account when considering the inclusion of other possible

⁴ These tests might not apply to all herbal substances and must be justified by the applicant.

pathogens (e.g. *Campylobacter* and *Listeria* species) in addition to those specified in the European Pharmacopoeia. Microbial counts should be determined using pharmacopoeial procedures or other validated procedures. The European Pharmacopoeia gives guidance on acceptance⁴ criteria.

– Mycotoxins (aflatoxins, ochratoxin A): The potential for mycotoxins contamination should be fully considered. For aflatoxins, procedure and acceptance criteria should follow pharmacopoeial precedents (2.8.18) and for ochratoxin A, the procedure is described (2.8.22) and acceptance criteria are given in specific monographs.

– Pesticides, Fumigation agents, etc.: The potential for residues of pesticides, fumigation agents etc. should be fully considered. Where necessary suitable validated methods should be used to control potential residues and the acceptance criteria should be justified. In the case of pesticide residues the acceptance criteria of the European Pharmacopoeia should be applied unless fully justified.

– Radioactivity: Radioactive contamination should be tested for if there are reasons for concerns.

Other appropriate tests⁴ (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 included to determine the content of the herbal substance. 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 are unknown, assays of analytical markers or other justified determinations are required. The appropriateness of the choice of markers should be justified. For example, reference to the assay of a marker in the relevant monograph of the European Pharmacopoeia is an appropriate justification.

3.2.2. Herbal preparations

Herbal preparations are also diverse in character ranging from simple, comminuted plant material to extracts, tinctures, oils and resins. A comprehensive specification must be developed for each herbal preparation based on recent scientific data. The general monograph 'Herbal drug preparations' of the European Pharmacopoeia 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). The ratio of the herbal substance to the genuine herbal preparation must be stated.

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.

⁴ These tests might not apply to all herbal substances and must be justified by the applicant.

d) Tests:

Water content: This test is important when the herbal preparations are known to be hygroscopic. 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), a detection procedure that is specific for water is required.

Impurities

– Residual solvents: Refer to the European Pharmacopoeia general text on Residual solvents for detailed information (or current VICH guidance on residual solvents).

– Inorganic impurities, toxic (heavy) metals: The need for inclusion of tests and acceptance criteria for inorganic impurities should be studied during development and based on knowledge of the plant species, whether it is wild or cultivated and the manufacturing process. The potential for manufacturing process to concentrate toxic residues should be fully addressed. If the manufacturing process will reduce the burden of toxic residues, the tests with the herbal substance may be sufficient. Acceptance criteria will ultimately depend on safety considerations. Where justified, procedures and acceptance criteria for Sulphated ash/Residue on ignition/Heavy metals (2.4.27) should follow pharmacopoeial precedents.

– Microbial limits: There may be a need to specify the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria. Microbial counts should be determined using pharmacopoeial procedures or other validated procedures. The European Pharmacopoeia gives guidance on acceptance⁴ criteria.

– Mycotoxins (aflatoxins, ochratoxin A): The potential for mycotoxins contamination should be fully considered. For aflatoxins, procedure and acceptance criteria should follow pharmacopoeial precedents (2.8.18) and for ochratoxin A, the procedure is described (2.8.22) and acceptance criteria are given in specific monographs.

– Pesticides, Fumigation agents, etc.: The potential for residues of pesticides, fumigation agents etc. should be fully considered. Where necessary suitable validated methods should be used to control potential residues and the acceptance criteria should be justified. In the case of pesticide residues, the acceptance criteria of the European Pharmacopoeia should be applied unless fully justified.

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. Where possible, a specific, stability-indicating procedure should be included to determine the content of the herbal substance in the herbal preparation. 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/VIS spectrophotometric assay is used for anthraquinone 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 marker should be justified.

⁴ These tests might not apply to all herbal substances and must be justified by the applicant.

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

The following tests and acceptance criteria are considered generally applicable to traditional herbal medicinal products for human use containing vitamins/minerals as ancillary substances:

- 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) (or VICH guideline 'Impurities in new veterinary medicinal products', CVMP/VICH/838/99 as revised) and the European Pharmacopoeia general text on Residual solvents (or current VICH guidance on residual solvents) for detailed information.

Impurities arising from degradation of the vitamin(s) or mineral(s) should be monitored in the traditional herbal medicinal product 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) and/or mineral(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.

3.2.4. Herbal medicinal products

The following tests and acceptance criteria are considered generally applicable to all herbal medicinal products:

- 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 herbal medicinal product 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 herbal medicinal products containing powdered or comminuted herbal substances, microscopical and macroscopical characterisation could be used for identification in combination with other methods, if justified.
- c) 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 included to determine the content of the herbal substance(s) and/or herbal preparation(s) in the herbal medicinal product. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For

example, where a UV/VIS spectrophotometric assay is used e.g. with anthraquinone glycosides a combination of the assay and a suitable test for identification (e.g. fingerprint chromatography) can be used.

In the case of herbal medicinal products 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. The choice of such markers should be justified. In cases where a specific assay of each active substance of a herbal medicinal product is not possible other justified determinations are required (for example, in multi-component traditional herbal medicinal products for human use the same markers may be present in more than one herbal substance/preparation).

d) Impurities:

Refer to the ICH/VICH guidelines on impurities in new drug products/guidelines on impurities in new veterinary medicinal products (CPMP/ICH/2738/99 and CVMP/VICH/838/99 as revised) and the European Pharmacopoeia general text on Residual solvents for detailed information.

- Impurities arising from the herbal substance(s) and/or herbal preparations e.g. contaminants such as pesticide/fumigant residues, toxic metals, if controlled during the testing of the herbal substance/preparation, it is not necessary to test for these in the herbal medicinal product.
- Similarly, residual solvent arising from the manufacture of the herbal preparation (e.g. an extract) need not be controlled in the herbal medicinal product provided it is appropriately controlled in the extract specification. However, solvents used for example in tablet coating will need to be controlled in the dosage form.
- In cases where degradation products of the herbal substance/preparation are evident (e.g. aglycones from hydroxyanthracene glycosides), they should be monitored in the herbal medicinal product.

Acceptance limits should be stated for such degradation products.

When it has been demonstrated conclusively by provision of a significant body of data, generated using appropriate analytical methodologies, that the herbal substance and/or herbal preparation do not degrade in the specific formulation and under the specific storage conditions proposed in the marketing authorisation, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

e) Microbial limits:

There is a need to specify the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria. These microbial counts should be determined using pharmacopoeial procedures or other validated procedures. The European Pharmacopoeia gives guidance on acceptance⁴ criteria (5.1.8 for herbal medicinal products for oral use and 5.1.4 for other herbal medicinal products).

3.3. Specific tests/criteria

In addition to the universal tests listed above, the following tests may be considered applicable to herbal medicinal products on a case-by-case basis. Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the herbal medicinal product for batch

control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

⁴ These tests might not apply to all herbal substances and must be justified by the applicant.

3.3.1. Herbal medicinal products

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

3.3.1.1. 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 herbal medicinal products 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 herbal medicinal product (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 must 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 $\pm 10\%$ of the labelled content of herbal substance or herbal preparation (i.e., a total variability of 20% : a requirement of $50\% \pm 10\%$ thus means an acceptable range from 40% to 60%), unless a wider range is supported by a bioequivalence study.

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 herbal medicinal product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

c) Uniformity of mass: The pharmacopoeial procedure should be used. 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 herbal medicinal product. In some cases, a Loss on drying procedure may be adequate; however, a detection procedure, which is specific for water (e.g., Karl Fischer titration) is required.

e) Microbial limits: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. It is advisable to test the herbal medicinal product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. For guidance on acceptable limits, reference should be made to the European Pharmacopoeia general text on the Microbiological Quality of Herbal Medicinal Products for Oral Use (5.1.8). Periodic testing may be appropriate.

Where appropriate, acceptance criteria should be set for the total count of aerobic micro-organisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas*). Counts should be determined using pharmacopoeial or other validated procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience. With acceptable scientific justification according to the Note for guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (CPMP/ICH/367/96) (or VICH GL39: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances, EMEA/CVMP/VICH/810/04), it may be possible to omit microbial limit testing for solid oral dosage forms.

3.3.1.2. 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.

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

c) Microbial limits: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. It is advisable to test the herbal medicinal product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. For guidance on acceptable limits, reference should be made to the European Pharmacopoeia general text on the Microbiological Quality of Herbal Medicinal Products for Oral Use (5.1.8). Periodic testing may be appropriate. With acceptable scientific justification, it may be possible to omit microbial limit testing for powders intended for reconstitution as oral liquids, according to the Note for guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (CPMP/ICH/367/96) (or VICH GL39: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances, EMEA/CVMP/VICH/810/04).

Where appropriate, acceptance criteria should be set for the total count of aerobic micro-organisms, total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas*). Counts should be determined by pharmacopoeial or other validated procedures, and at a sampling frequency or time point in manufacture, which is justified by data and experience.

d) Antimicrobial preservative content: For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content must be stated. 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 European Pharmacopoeia 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 throughout the 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' (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: Generally, where development and stability data show no significant evidence of extractables 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 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) Alcohol content: Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be 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 lot 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 lot 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 lot testing or elimination of this attribute from the specification.

n) Water content: For oral products requiring reconstitution, a test and 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.

3.3.1.3. Herbal Medicinal Products containing exclusively herbal substances (e.g. herbal teas)

One or more of these tests may be applicable to herbal medicinal products containing exclusively herbal substances.

a) Loss on drying: To be specified depending on the plant parts present in the herbal medicinal product, if not performed on the herbal substance.

b) Identification: Identification tests (e.g., chromatographic methods) must establish the specific identity of the herbal substance(s) in the herbal medicinal product and optimally should be discriminatory between the different herbal substances and with regards to substitutes/adulterants that are likely to occur. Microscopical and macroscopical characterisation can be used to support identification, if justified.

c) Purity: Relevant adulterants and substitutes should be determined (e.g., when toxic adulterants or substitutes are known).

d) 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. 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.

e) Assay: In the case of such herbal medicinal products 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 possible, a specific, stability-indicating procedure should be included to determine the content of the herbal substance(s) in the herbal medicinal product. 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/VIS 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 herbal medicinal products consisting of one herbal substance without any excipients, the assay can be included in the specification of the herbal substance, if justified.

Finally, in cases of multi-component herbal medicinal products where an assay of each herbal substance is not possible, the applicant must justify how reproducibility of the finished product is guaranteed and tested.

f) Particle size: A suitable specification has to be given by the manufacturer.

g) Microbial quality: Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. It is advisable to test the herbal medicinal product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. Reference should be made to the European Pharmacopoeia general text on the Microbiological Quality of Herbal Medicinal Products for Oral Use (5.1.8) for guidance on acceptable limits. Periodic testing may be appropriate. Where appropriate, acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas*). Counts should be determined using pharmacopoeial or other validated procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience.

4. Definitions

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

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 herbal medicinal product.

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/herbal medicinal products in general only toxicologically relevant degradation products must 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.

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

Genuine (Native) 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.

Ratio of herbal substance to genuine herbal preparation (DER genuine): is the ratio of the mass of the herbal substance to the quantity of the resulting genuine herbal preparation. 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.

Herbal medicinal products: 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: 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 Herbal Medicinal Product 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.

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 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 herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal substance/preparation and/or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specific test: A test which is considered to be applicable to a particular herbal substance/preparation or a particular herbal medicinal product 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: are medicinal products for human use, that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

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.