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NOTE FOR GUIDANCE ON SPECIFICATONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR HERBAL DRUGS, HERBAL DRUG PREPARATIONS AND HERBAL MEDICINAL PRODUCTS (FORMERLY CPMP/HMPWP/19/99)

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NOTE FOR GUIDANCE ON SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR HERBAL DRUGS, HERBAL DRUG PREPARATIONS AND HERBAL MEDICINAL PRODUCTS

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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 drug preparations (herbal drugs) and herbal medicinal products to support applications for marketing authorisations and should be read in conjunction with the Note for guidance on quality of herbal medicinal products (CPMP/QWP/2819/00 and EMEA/CVMP/814/00)

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 drug preparation (herbal drug) or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal drug preparation (herbal drug) and 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 drug preparation (herbal drug) 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 Good Agriculture Practice and Good Manufacturing Practice, 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 starting plant material (herbal drug), to the herbal drug preparation and to the finished herbal medicinal product. Specifications are primarily intended to define the quality of the herbal drug preparation (herbal drug) 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 drug preparation (herbal drug) and herbal medicinal product.

1.3. Scope of the guideline

The quality of herbal drug 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 drug preparations (herbal drug) 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 drug preparations (herbal drugs) 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 drug preparations (herbal drugs) or herbal medicinal products during the clinical research stages of drug 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 drug preparations (herbal drugs) and herbal medicinal products, i.e. universal acceptance criteria,

and those which are considered specific to individual herbal drug preparations (herbal drugs) 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 technology, and modifications to existing technology, 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 drug preparation (herbal drug) or herbal medicinal product (which includes a detailed evaluation of the botanical and phytochemical aspects of the plant, manufacture of the preparation and the finished 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 distinquish the active plant from potential adulterants and substitutes.

2.1.2. Phytochemical characterisation

Analytical research of constituents including active constituents as well as compounds suitable as marker substances. Includes chromatographic fingerprinting.

2.1.3 Potential Impurities/Contaminants/Degradation Products

This includes aspects such as heavy metals, pesticides, fumigants etc.

2.1.4 Biological variation

Includes historical batch data and published information concerning biological variation.

2.2. Design and development considerations

The experience and data accumulated during the development of a herbal drug preparation (herbal drug) 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 drug or herbal drug 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 drug 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 extracts or tinctures depending on the ethanol content if justified by scientific evidence.

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 drugs, herbal drug preparations and their finished 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. This concept may therefore 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 only and not to herbal drugs or herbal drug preparations. 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 drug 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 drug preparation (herbal drug) 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 drug, a sample of the herbal drug preparation e.g. extract or tincture or a chemically defined substance e.g. a known active constituent, a marker substance or a known impurity. The reference standard has a quality appropriate to its use. The composition of reference standards of herbal drugs and herbal drug 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 drug 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 drug, herbal drug preparation and herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal drug preparation (herbal drug) 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 drug preparation (herbal drug) 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 drug preparation (herbal drug) 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 drugs are linked to:

  botanical characteristics of the plant part
  phytochemical characteristics of the plant part - known therapeutic constituents, toxic constituents (identity, assay, limit tests)
  biological /geographical variation
  cultivation/harvesting/drying conditions (microbial levels, aflatoxins, heavy metals etc)
  pre-/post-harvest chemical treatments (pesticides, fumigants)
  profile and stability of the constituents

- Specifications for herbal drug preparations are linked to:

  quality of the herbal drug (as above)
  method of preparation from the herbal drug
  drying conditions (e.g. microbial levels, residual solvents in extracts)
  profile and stability of the constituents
  microbial stability
  batches used in pre-clinical/clinical testing (safety and efficacy considerations)

- Specifications for herbal medicinal products are linked to:

  quality of the herbal drug and/or herbal drug preparation
  manufacturing process (temperature effects, residual solvents)
  profile and stability of the active constituents/ 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 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 active substances and medicinal products (CPMP/ICH/380/95 and CVMP/VICH/899/99) and the Note for guidance on Stability Testing of existing Active Substances and Related Finished Products (CPMP/QWP/556/96 and EMEA/CVMP/846/99).

3.2. Universal tests/criteria

Implementation of the recommendations in the following section should take into account the ICH /VICH Guidelines „Text on Validation of Analytical Procedures“ and „Validation of Analytical Procedures: Methodology (CPMP/ICH/281/95 and CVMP/VICH/591/98).

3.2.1. Herbal drugs

Herbal drugs are a diverse range of botanical materials including leaves, herbs, roots, flowers, seeds, bark etc. A comprehensive specification must be developed for each herbal drug even if the starting material for the manufacture of the finished product is a herbal drug preparation. In the case of fatty or essential oils used as active substances of herbal medicinal products a specification for the herbal drug 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 drugs.

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 drug is obtained.

b) Characters: a qualitative statement about the organoleptic character(s) where characteristic and the macroscopic and microscopic botanical characters of the herbal drug.

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 drug and are usually a combination of three or more of the following:

   Macroscopical characters
   Microscopical characters
   Chromatographic procedures
   Chemical reactions

c) Tests

- Foreign matter
- Total Ash
- Ash Insoluble in hydrochloric acid[1]
- Water soluble extractive[1]
- Extractable matter[1]

[1] These tests might not all apply to herbal drugs and must be justified by the applicant.

- Particle size: For some herbal drugs 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 drugs are known to be hygroscopic. For non-pharmacopoeial herbal drugs, 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.
- Inorganic impurities, toxic 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, its cultivation and the manufacturing process. Acceptance criteria will ultimately depend on safety considerations. Where justified, procedures and acceptance criteria for sulfated ash / residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.
- 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 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 acceptance criteria.
- Mycotoxins: The potential for mycotoxins contamination should be fully considered. Where necessary suitable validated methods should be used to control potential mycotoxins and the acceptance criteria should be justified.
- 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 method, acceptance criteria and guidance on the methodology of the European Pharmacopoeia should be applied unless fully justified.
- Other appropriate tests[1] (e.g. swelling index)

d) Assay:

In the case of herbal drugs with constituents of known therapeutic activity, 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 drug. 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 determination of essential oils is adopted to assay the herbal drug, the combination of the assay and a suitable test for identification (e.g. fingerprint chromatography) can be used.

[1] These tests might not all apply to herbal drugs and must be justified by the applicant.

In the case of herbal drugs where the constituents responsible for the therapeutic activity are unknown assays of marker substances or other justified determinations are required. The appropriateness of the choice of marker substance should be justified.

3.2.2. Herbal drug preparations

Herbal drug 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 drug 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 drug 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 drug to the herbal drug preparation must be stated.

b) Characters: a qualitative statement about the organoleptic characters of the herbal drug preparation where characteristic

c) Identification: Identification tests should be specific for the herbal drug 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.

d) Tests:

- Residual solvents: Refer to the European Pharmacopoeia Monograph *Residual Solvents* for detailed information.
- Water content: This test is important when the herbal drug 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.
- Inorganic impurities, toxic 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, its cultivation 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 drug may be sufficient. Acceptance criteria will ultimately depend on safety considerations. Where justified, procedures and acceptance criteria for sulfated ash / residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, e.g. atomic absorption spectroscopy.
- 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. These limits should comply with those in the European Pharmacopoeia.

- Mycotoxins: The potential for mycotoxins contamination should be fully considered. Where necessary suitable validated methods should be used to control potential mycotoxins and the acceptance criteria should be justified.
- 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 method, acceptance criteria and guidance on the methodology of the European Pharmacopoeia should be applied unless fully justified.

e) Assay:
In the case of herbal drug preparations with constituents of known therapeutic activity, 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 drug in the herbal drug preparation. 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 visible UV 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 drug preparations where the constituents responsible for the therapeutic activity are unknown, assays of marker substances or other justified determinations are required. The appropriateness of the choice of marker substance should be justified.

3.2.3. 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 drug(s) and/or herbal drug 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.

c) Assay:
In the case of products containing herbal drugs and/or herbal drug preparations with constituents of known therapeutic activity, validated assays of the content of these consituents 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 drug(s) and/or herbal drug preparation(s) in the finished 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 visible UV 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 products containing herbal drug(s) and/or herbal drug preparations where the constituents responsible for the therapeutic activity are unknown, assays of marker substances or other justified determinations are required.

d) Impurities:
Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH/VICH Guidelines on Impurities in New Drug Products (ICH/282/95 and CVMP/VICH/838/99) and the European Pharmacopoeia Monograph Residual Solvents for detailed information.

- Impurities arising from the herbal drug(s) and/or herbal drug preparations e.g. contaminants such as pesticide/fumigant residues, heavy metals, are normally controlled during the testing of the herbal drug preparation (herbal drug) and it is not necessary to test for these in the herbal medicinal product.
- Similarly, residual solvent arising from the manufacture of the herbal drug preparation (e.g. an extract) need not be controlled in the finished 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.
- Major impurities arising from degradation of the herbal drug preparation (herbal drug) should be monitored in the herbal medicinal product. Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products.

  When it has been demonstrated conclusively by provision of a significant body of data, generated using appropriate analytical methodologies, herbal drug(s) and/or herbal drug preparation(s) 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.
- 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 limits should comply with the European Pharmacopoeia. The frequency of testing should be justified.

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.

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 and without constituents with known therapeutic activity, the test for in-vitro active ingredient release can be omitted.

For immediate release products containing herbal drug 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 ±10% of the labelled content of herbal drug or herbal drug 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 supported by a bioequivalency 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 dosage units: This term includes both uniformity of content and uniformity of mass; a pharmacopoeial procedure should be used. If appropriate, these tests may be performed as in-process controls; the acceptance criteria should be included in the specification.

d) Water content: A test for water content should be included when appropriate. The acceptance criteria 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. Reference should be made to the European Pharmacopoeia general text on the *Microbiological Quality of Pharmaceutical Preparations* for guidance on acceptable limits. 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, 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 dosage units: This term includes both uniformity of content and 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. Reference should be made to the European Pharmacopoeia general text on

the Microbiological Quality of Pharmaceutical Preparations for guidance on acceptable limits. 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.

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 micro-organisms 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 Note for guidance on Stability Testing of existing Active Substances and Related Finished Products (CPMP/QWP/556/96 and EMEA/CVMP/846/99), 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.

e) Alcohol content: Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified.

f) Dissolution: In addition to the attributes recommended immediately above, it may be appropriate (e.g. where constituents of the herbal drug or herbal drug 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.

h) 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.

i) 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 resuspension 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.

j) 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.

k) 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.

l) 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.

m) 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.

4. GLOSSARY

Herbal medicinal products: are medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations.

Herbal drugs: are mainly whole, fragmented or cut, plants, parts of plants, algae, fungi, lichen in an unprocessed state, usually in dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal drugs. Herbal drugs are precisely defined by the botanical scientific name according to the binomial system (genus, species, variety and author).

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

Native herbal drug preparation: refers to the preparation without excipients.

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

Fixed combination: A herbal medicinal product which contains more than one herbal drug preparation or herbal drug.

Degradation product: Degradation products are molecular variants resulting from changes in the desired product or product-related substances brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of processing and/or storage (e.g. deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances or product-related impurities.

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

Identified impurity: An impurity for which a structural characterisation has been achieved.

Quality: The suitability of either a herbal drug preparation (herbal drug) or herbal medicinal product for its intended use. This term includes such attributes as the identity, strength, and purity of the article.

Reagent: A substance other than a starting material or solvent, which is used in the manufacture of a herbal drug preparation (herbal drug).

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of a herbal drug preparation (herbal drug) 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 drug preparation (herbal drug) or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal drug preparation (herbal drug) 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 particular herbal drug preparation (herbal drug)s or particular herbal medicinal products depending on their specific properties and/or intended use.

Specified impurity: An identified or unidentified impurity that is selected for inclusion in the herbal drug preparation (herbal drug) or herbal medicinal product specification and is individually listed and limited in order to assure the quality of the herbal drug preparation (herbal drug) or herbal medicinal product.

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 drug preparations (herbal drug), or all herbal medicinal products; e.g., appearance, identification, assay, and impurity tests.