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FINAL

GUIDELINE ON QUALITY OF COMBINATION HERBAL MEDICINAL PRODUCTS[1] / TRADITIONAL HERBAL MEDICINAL PRODUCTS

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

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GUIDELINE ON QUALITY OF COMBINATION HERBAL MEDICINAL PRODUCTS / TRADITIONAL HERBAL MEDICINAL PRODUCTS

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EXECUTIVE SUMMARY

This guideline applies to herbal medicinal products containing combinations of herbal substances and/or herbal preparations[2]. The quality of a combination herbal medicinal product should be guaranteed and demonstrated in accordance with the existing requirements as set out in: Annex I to Directive 2001/83/EC as amended, Annex I to Directive 2001/82/EC as amended and with current EU/(V)ICH guidelines on quality.

For some combination products, identification and assay of individual herbal substances / herbal preparations in the herbal medicinal product is difficult to perform and sometimes impossible. In those situations, the specific provisions set out by the existing legislation and guidelines need to be considered further.

This guideline addresses in more detail the approaches for identification and quantitative determination of herbal substances and/or herbal preparations in combination herbal medicinal products taking into account their complex composition and the potential for interference in analysis by other herbal substances/preparations present in the herbal medicinal product. In principle, the identity and the quantity of the active substances in the herbal medicinal product should be demonstrated. Where a comprehensive analysis of each active substance is not possible even when the specific provisions foreseen in existing guidelines are used, specific emphasis may be placed on the validation and design of the manufacturing process and detailed documentation of each critical step in addition to more global tests of identity and of quantity in the herbal medicinal product. For these products batch-to-batch consistency in quality has to be reached through appropriate manufacture of the herbal medicinal product and in particular in the choice of the in process controls [IPC] and appropriate testing of the herbal medicinal product. A comprehensive justification should be provided by the applicant for the approach taken.

In these situations it is recommended that applicants consult the relevant Competent Authority for further guidance.

1. INTRODUCTION (background)

Herbal medicinal products can be combinations of herbal substances and/or herbal preparations. In most cases herbal substances are extracted separately and then mixed in the herbal medicinal product. However in some instances herbal substances are mixed before extraction.

In most authorised combination herbal medicinal products only a limited number of active substances are combined. However, following full implementation of the simplified registration procedure for traditional herbal medicinal products for human use, established by Directive 2004/24/EC, it is expected that the number of applications for combination products will increase.

It should be noted that the quality of a medicinal product is independent of its use and therefore all general principles of quality and quality guidance are applicable to all herbal medicinal products. Furthermore, the specific herbal quality guidelines are applicable to all herbal medicinal products. However, the complexity of combination products may have an important impact on the quality control measures to be put in place in order to ensure and demonstrate batch-to-batch consistency in quality. Clarification on how the existing requirements should be interpreted in order to demonstrate quality of combination herbal medicinal products is needed.

This guideline takes into account the European Pharmacopoeia monographs on herbal substances and herbal preparations.

[2] The term “herbal substance” should be considered as equivalent to the term “herbal drug” as defined in the European Pharmacopoeia and the term “herbal preparation” should be considered as equivalent to the term “herbal drug preparation” as defined in the European Pharmacopoeia.

2. SCOPE

This guideline applies to herbal medicinal products containing combinations of herbal substances and/or herbal preparations. The quality, including stability, of a combination herbal medicinal product should in general be guaranteed and demonstrated in accordance with the existing quality guidance.

This guideline addresses the approaches for identification and quantitative determination of herbal substances/preparations in combination herbal medicinal products, taking into account the complex composition of the herbal medicinal product. Most combination herbal medicinal products with marketing authorisation have only a limited number of active substances. The specifications are based on the clinical data presented to support the application and full testing is expected in accordance with the current quality guidance. However, in most EU countries the majority of products containing multiple active substances are traditional herbal medicinal products. The specifications of a traditional herbal medicinal product are not required to be based on a clinically tested product but are based on a product with a long-standing use. Due to the complexity of products containing multiple active substances, compliance with the existing EU guidelines on quality can be difficult to demonstrate. Although this is addressed by specific provisions in existing guidance, additional clarification and practical guidance on interpretation need to be provided.

This guideline should be read in conjunction with the "Guideline on quality of herbal medicinal products/traditional herbal medicinal products" (1), "Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products" (2), Annex 7 "Manufacture of herbal medicinal products" of Good Manufacturing Practices (GMP) for medicinal products, Volume 4, Rules governing medicinal products in the European Union (3), the "Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products in the SPC (4), the "Guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin (5) and the "Concept paper on quality of combination herbal medicinal products / traditional herbal medicinal products" (6).

The additional presence of vitamins and/or minerals in traditional herbal medicinal products is not addressed in this guideline. Reference is made in this regard to the general quality guidance for active substances and medicinal products. It is however clear that the presence of vitamins and/or minerals in traditional herbal medicinal products does not exclude such products from the scope of this guideline.

3. LEGAL BASIS

This guideline supports applications for marketing authorisations according to Directive 2001/82/EC, as amended and Directive 2001/83/EC, as amended.

A simplified registration procedure was established for traditional herbal medicinal products under Directive 2001/83/EC, as amended by Directive 2004/24/EC. This guideline applies equally to traditional herbal medicinal products for human use.

4. MAIN GUIDELINE TEXT

Herbal medicinal products contain herbal substances/preparations each consisting of a large number of chemical constituents of which only a few may be characterized. Furthermore, herbal substances are natural in origin and consequently their chemical composition varies. In addition, in most cases the constituents responsible for the therapeutic activity are unknown or only partly explained and often markers are used to characterize these products.

In herbal medicinal products containing combinations of herbal substances and/or herbal preparations, quality control may be more problematic because, in addition to the above-mentioned difficulties, other herbal substances and/or preparations may interfere with the analysis, e.g. extraction or detection of a marker may be affected by other herbal substances present (co-elution) in the herbal medicinal product.

The quality of a combination herbal medicinal product should in general be guaranteed and demonstrated in accordance with the existing guidance. All relevant parameters should be tested in the herbal medicinal product and identification and assay of each herbal substance/herbal preparation

included in the product are required. The stability of the herbal medicinal product must be guaranteed. For some combination herbal medicinal products, identification and –quantitative determination of individual herbal substances/herbal preparations in the product are difficult to perform and sometimes impossible. Clarification on how the requirements on identification and assay should be interpreted is provided below. It should be stressed that notwithstanding the guidance given, all analytical methods usually applied for identification and assay should be investigated first, e.g. the methods described in the Ph. Eur. General Chapter 2 "Methods of analysis". Furthermore, each approach taken should be justified by the applicant, and should take into account the combination herbal medicinal product that is subject of the application.

If individual active substance testing for identity, assay or to demonstrate stability cannot be performed in the herbal medicinal product, alternative strategies may be considered. The simple omission of (a) test(s) is not acceptable as the quality of combination herbal medicinal products should be comparable to the quality of other (herbal) medicinal products. In this regard, reducing the number of active substances in the herbal medicinal product could increase the possibilities to perform all tests (e.g. identification, assay etc.) in the herbal medicinal product. As required for all medicinal products, GMP, process validation and batch records documenting each step in the manufacturing process of the herbal medicinal product and including results of IPC testing should ensure that, in combination with suitable testing criteria, a product of good and consistent quality is obtained. The manufacturing process should, as required for all medicinal products, be designed in such a way that the manufacture and composition of the herbal medicinal product is well-controlled and conforms with the declared composition. The manufacturing process design should be supported by well-documented process validation. An appropriate IPC testing programme (e.g. testing at various points during the stepwise addition of the herbal substances/preparations) and an identification test of the herbal substance/herbal preparation immediately before the introduction in the manufacturing process of the herbal medicinal product are measures to ensure the consistent quality and declared composition of the herbal medicinal product. Each step of the manufacturing process should be regarded as critical and appropriate procedures to ensure correct addition of active substances and/or excipients should be in place as routine control. Documentation on GMP should be available to the Competent Authorities upon inspection, and manufacturing and process validation data should be submitted in the marketing authorisation/registration dossier.

Where a joint assay is performed, the active substance specification should include a limit for the common marker (additional, if different from the pharmacopoeial marker) to ensure its recovery in the herbal medicinal product.

Where applicable, the same principles apply to control tests carried out at an intermediate stage of the manufacturing process of the herbal medicinal product.

The following requirements apply for identification and quantitative determination of **<u>each</u>** active substance in the combination herbal medicinal product:

IDENTIFICATION TEST OF EACH ACTIVE SUBSTANCE (read in conjunction with Decision tree # 1: Identification test of each active substance in combination herbal medicinal products)

- *where constituents with known therapeutic activity or active markers of the herbal substance / preparation are known*, the idenfication of the active constituents should be performed in the herbal medicinal product in accordance with the Guideline on specifications (2).

- *where constituents with known therapeutic activity or active markers of the herbal substance/preparation are not known*:

    - Each herbal substance/preparation that can be identified should be identified in the herbal medicinal product in accordance with the Guideline on specifications (2).

    - Where the herbal substance/preparation cannot be identified in the herbal medicinal product, appropriate justification and documentation that all analytical methods usually applied for identification, e.g. the methods described in the Ph. Eur. General

Chapter 2 “Methods of analysis”, have been investigated should be provided. Furthermore:

- The identification test of the herbal substance/preparation should be performed as an in process control at the latest point in the manufacturing process of the herbal medicinal product where analysis is still possible. The approach taken should be justified by the applicant. The identification test should be supported by documented evidence on the manufacture of the herbal medicinal product batch (batch records) and process validation.

  In addition, the release specifications of the herbal medicinal product should include suitable identification methods for the combination, e.g. characteristic fingerprints, in line with the Guideline on specifications (2). The sum of the identification methods should allow appropriate characterisation of the combination.

- If IPC testing of the herbal substance/preparation is not possible, it is required that the herbal substance/preparation is identified according to its specifications immediately before the introduction of the active substance in the manufacture of the herbal medicinal product. The approach taken should be justified by the applicant. The identification test should be supported by documented evidence on the manufacture of the herbal medicinal product batch (batch records) and process validation. The applicant specifies and justifies which information is submitted in the application in order to document quality, and which documentation is available upon inspection by the Competent Authorities.

  In addition, the release specifications of the herbal medicinal product should also include suitable identification methods, e.g. characteristic fingerprints in line with the Guideline on specifications (2). The sum of the identification methods should allow appropriate characterisation of the combination.

ASSAY OF EACH ACTIVE SUBSTANCE (read in conjunction with Decision tree # 2: Assay of each active substance in combination herbal medicinal products)

- *where constituents with known therapeutic activity or active markers of the herbal substance/preparation are known,*
  - an individual assay of the active substance should be performed in the herbal medicinal product in accordance with the Guideline on specifications (2).
  - If an individual assay of the herbal substance/preparation is not possible, the quantitative determination can be carried out jointly for two or more herbal substances/preparations (e.g. joint determination of group of anthraquinone-derivatives) in accordance with the Guideline on specifications (2).
- *where constituents with known therapeutic activity or active markers of the herbal substance/preparation are not known:*
  - Each herbal substance/preparation that can be assayed, should be assayed in the herbal medicinal product in accordance with the Guideline on specifications (2).
  - If an individual assay of the herbal substance/preparation is not possible, the quantitative determination can be carried out jointly for two or more herbal substances/preparations in accordance with the Guideline on specifications (2).

    An assay of a common marker gives limited information on the relative composition of the concerned herbal substances/preparations in the herbal medicinal product. As

such, markers for joint analysis should be carefully selected and justified. If a joint analysis is considered acceptable, the specifications of the concerned herbal substances/preparations should include a (additional, if different from the pharmacopoeial marker) limit for the common marker. The approach taken should be justified by the applicant. Each approach should be supported by careful process validation and documentary evidence should be available.

- Where the herbal substance/preparation cannot be assayed in the herbal medicinal product, appropriate justification and documentation that all analytical methods usually applied for assay , e.g. the methods described in the Ph. Eur. General Chapter 2 "Methods of analysis", have been investigated should be provided.

  Furthermore, an appropriate manufacturing process design, supported by strict and well-documented process validation, should ensure that the manufacture and quality of the herbal medicinal product is well-controlled and that the composition of the herbal medicinal product conforms with the declared composition. The manufacturing process development studies (e.g. analytical profiles during the stepwise addition of the herbal substances/preparations, degradation studies during the manufacture of the herbal medicinal product) and other studies [e.g. stability studies of the active substance(s)] are pivotal in this regard and should underpin the proposed approach to ensure the quality and composition of the herbal medicinal product e.g. assay of the active substance as IPC. The approach taken should be justified by the applicant. Tests should be supported by documented evidence on the manufacture of the herbal medicinal product batch (batch records).

  In addition, the release and shelf life specification of the combination should include suitable assay methods for the combination in line with the Guideline on specifications (2), including e.g. semi-quantitative fingerprints, allowing a characteristic quantitative determination of the combination.

The requirements above apply to the identification and quantitative determination of each herbal substance/preparation in a combination herbal medicinal product. The overall release and shelf life specifications of a combination herbal product will therefore in general be a mixture of tests that individually identify and assay the herbal substance(s)/preparation(s) in the herbal medicinal product and/or tests that jointly assay herbal substances/preparations in the herbal medicinal product, and all other suitable identification tests and assays that allow an appropriate characterisation and a characteristic quantitative determination of the combination.

Stability of the herbal medicinal product

The stability of the combination herbal medicinal product should be determined in accordance with existing guidance on stability and the specific herbal guidelines (1, 2).

For an herbal medicinal product containing herbal substances/preparations where constituents with known therapeutic activity or active markers are known, the appropriate stability of these active constituents must be demonstrated (Decision Tree #2).

In accordance with the Guideline on the quality of the herbal medicinal product, if a herbal medicinal product contains combinations of several herbal substances and/or herbal preparations, and if it is not possible to determine the stability of each active substance, the stability of the combination has to be demonstrated by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical or other appropriate tests. The appropriateness of the tests shall be justified by the applicant (1).

DEFINITIONS

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 an herbal substance, an herbal preparation or an herbal medicinal product.

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).

In Process Control (IPC): controls performed during manufacture of the medicinal product (finished product) in order to monitor and if necessary to adjust the process to ensure that the medicinal product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of an in process control.

Example: testing at various points during the stepwise addition of the herbal substances/preparations

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

There are two categories of markers:

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

Analytical marker: are constituents or groups of constituents that serve for analytical purposes.

Specifications: 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 an herbal preparation / herbal substance or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal preparation / herbal substance 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.

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.

REFERENCES

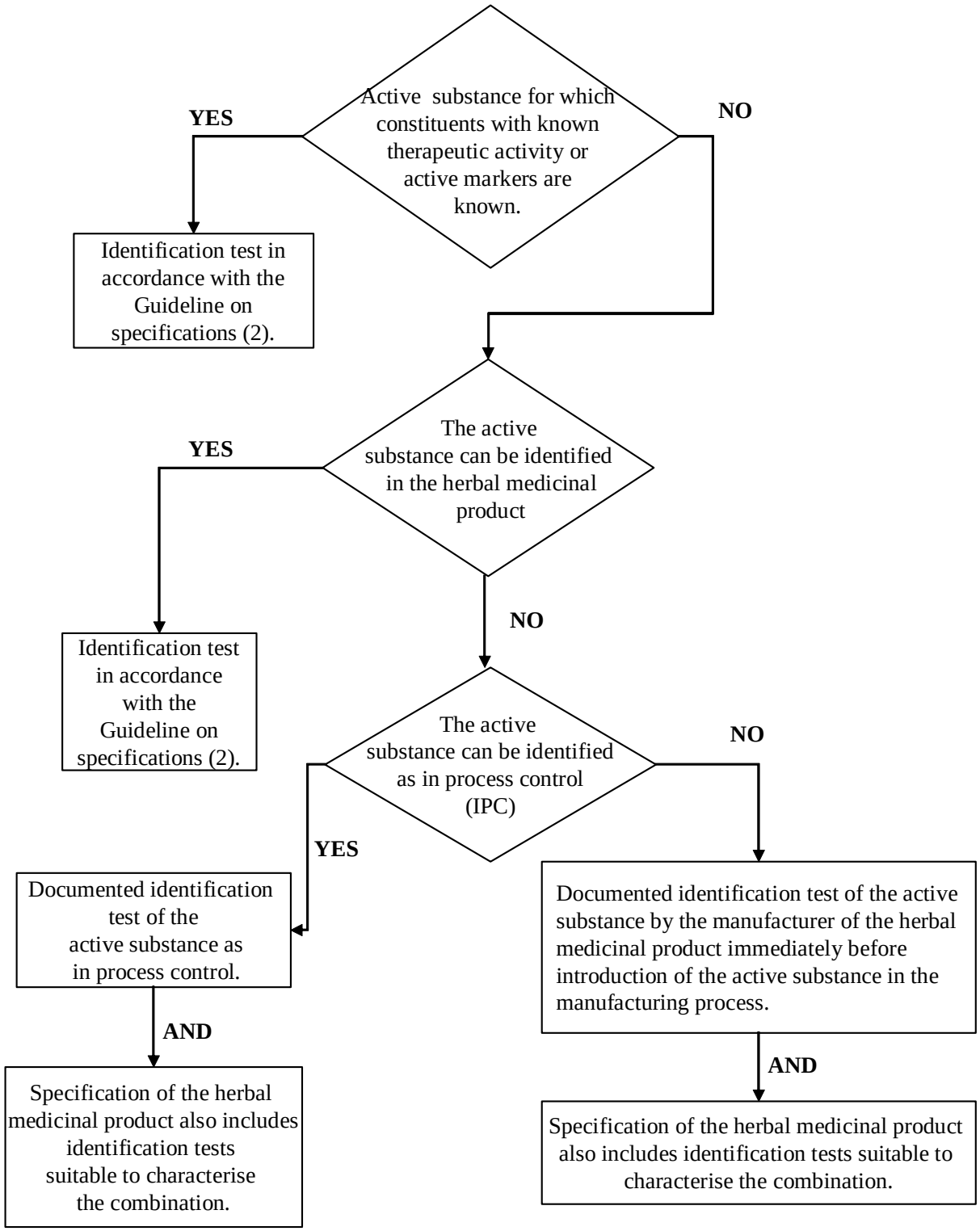
1. ‘Guideline on quality of herbal medicinal products/traditional herbal medicinal products’ (CPMP/QWP/2819/00, EMEA/CVMP/814/00, current version).
2. ‘Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products’ (CPMP/QWP/2820/00, EMEA/CVMP/815/00, current version).

3. Annex 7 “Manufacture of herbal medicinal products” of Good Manufacturing Practices (GMP) for medicinal products, Volume 4, Rules governing medicinal products in the European Union, current version.
4. ‘Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products in the SPC’
(EMEA/HMPC/CHMP/CVMP/287539/2005, current version)

5. ‘Guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin’ (EMEA/HMPC/246816/2005, current version)

6. ‘Concept paper on quality of combination herbal medicinal products traditional herbal medicinal products’ (EMEA/HMPC/CHMP/CVMP/58222/2006)

Decision tree # 1
Identification test of each active substance in combination herbal medicinal products



Decision tree # 2
Assay of each active substance in combination herbal medicinal products