



CONTENT OF THE DOSSIER FOR HERBAL DRUGS AND HERBAL DRUG PREPARATIONS QUALITY EVALUATION

Addendum to the Certification PROCEDURE AP-CSP-93 (5) as amended

INTRODUCTION

The quality of herbal drugs and herbal drug preparations is determined by the quality of the starting plant material, development and in-process controls, application of GMP controls and process validation, and by specifications applied throughout development and production / manufacture. This document addresses information to be provided for an application dossier for a certificate of suitability as defined in the resolution AP-CSP (93) 5 as amended. This should be read in conjunction with the *Note for guidance on specifications: test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products (CPMP/QWP/2820/00)* and the *Note for guidance on quality of herbal medicinal products (CPMP/QWP/2819/00)*.

The scope of the general European Pharmacopoeia monographs on Herbal Drugs (n°1433) and Herbal drug preparations (n°1434) is defined as follows¹:

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

SAMPLES

Together with the dossiers the applicant shall provide the Certification Unit of the EDQM with samples of 1 or 2 representative commercial batches in sufficient quantity to perform a complete analysis. Reference standards and/or samples of impurities are required if revision of the monograph is requested and/or if an additional method(s) to limit the related substances is (are) appended to the certificate for possible checking by the laboratory of the EDQM.

¹ The term of "Herbal Drug" shall be considered to be equivalent to the term "Herbal Substances" as defined in the Notice to applicant, Vol 2B-CTD, modules 3-4, Edition 2001.

The term of "Herbal Drug Preparation" shall be considered to be equivalent to the term "Herbal Preparation" as defined in the Notice to applicant, Vol 2B-CTD, modules 3-4, Edition 2001.



ADMINISTRATIVE FORM

Complete name(s) and address(es) of intended holder, producer(s) and manufacturing site(s)

In special cases where the holder of the certificate will not be the producer / manufacturer, **an formal agreement signed** by both parties shall be provided, stating that the producer / manufacturer wishes not to be the holder and commits itself to provide the necessary information to its authorised agent.

History of the product

Where applicable: Length of time on the market of the herbal drug / herbal drug preparation marketed by the applicant in accordance with the application presented as an ingredient in products approved by a competent authority in member countries of the European Pharmacopoeia Convention or in any other country; the countries in which it has been used; and the medicinal products in which it has been used.

Declaration

A signed declaration that production / manufacture is conducted in accordance with the dossier presented and with a specified guideline on GMP for starting materials. Official international and national guidelines as available should be applied. Such guidance should be read in conjunction with EMEA Herbal Medicinal Products Working Party document “*Points to consider on good agricultural and collection practice for starting materials of herbal origin* (EMEA/HMPWP/31/99 Rev.3). Other approaches to GMP of similar standards (Good Agricultural Practices) are acceptable, if justified. The producer should indicate in the dossier which guidelines are referred to.

A signed declaration that the producer / manufacturer is willing to be inspected, on the request of a relevant authority before and/or after being granted a certificate of suitability. In cases where the applicant is not the producer, this declaration should also be provided by the authorised agent.

PRESENTATION OF THE APPLICATION DOSSIER:

The application should be presented in accordance-for each section-with the numbering and terminologies of the Notice to Applicant, Vol 2B-CTD, module 3-4, Edition 2001.

HERBAL DRUG

General information (3.2.S.1)

Nomenclature (3.2.S.1.1):

The European Pharmacopoeia Monograph name, the scientific botanical name according to the binomial system (genus, species, variety and author) and the common name if used for the labeling (together with the Ph.Eur. name) should be stated together with any laboratory code used in the dossier.

Structure (3.2.S.1.2):

As per CTD

Production/process (3.2.S.2)



Producer(s) (3.2.S.2.1):

The name and address of the intended producer(s) and the proposed site(s) or facility(ies) involved in the production process should be provided. Other parties than the intended producer(s) may be mentioned on the certificate where relevant: e.g. if other parties are involved in certain stages of the process; in this case(s) details of their involvement and of other site addresses must be provided and information given on the contractual arrangements regarding sole or shared responsibilities. If an additional source is used to provide, alternative capacity information must be provided to demonstrate that the alternative arrangements yield material of the same quality as that produced by the first source.

Description of manufacturing process and Process Controls (3.2.S.2.2):

Information should be provided to adequately describe the plant production and plant collection, including:

- Geographical source of herbal drug
- Cultivation, harvesting, drying and storage conditions
- Pre- and post- harvest chemical treatments e.g. pesticides, fumigants
- Any other treatment.

Characterisation (3.2.S.3)

Information should be provided on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity if necessary.

This should also include additional features which distinguish the active plant from potential adulterants and substitutes in case the monograph does not suitably cover that aspect.

Impurities (3.2.S.3.2):

Possible impurities originating from the production or from degradation where applicable should be listed and discussed with an indication of their origin. If alternative production processes / sources are described the possible impurities are discussed separately for each route.

- a) Starting material
- b) Discrimination between related species, where relevant
- c) Potential adulterants / substitutes / contaminants that are likely to be present.
- d) Foreign organic matter
- e) Inorganic impurities, toxic metals: The need for inclusion of tests and acceptance criteria for inorganic impurities should be studied during the development and based on the knowledge of the plant species, its cultivation and the production process. Acceptance criteria will ultimately depend on safety considerations. Where justified procedures and acceptance criteria for sulphated ash / residue on ignition should follow pharmacopoeial precedents, other impurities may be determined by other appropriate procedures, e.g. atomic absorption, and appropriate limit set up.
- f) 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 are to be applied wherever appropriate.

- g) Radioactivity: This should be tested if there are reasons for concerns.
- h) Water content: This test is important when the herbal drugs are known to be hygroscopic.

NB: A loss on drying procedure may be adequate. In some cases (essential oil containing plants) a detection procedure that is specific to water is required.

- i) Microbial limits: There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and moulds, and the absence of specific objectionable bacteria. These limits should comply with those of the Ph.Eur.
- j) 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.
- k) Degradation products, where relevant

The ability of the methods of the monograph of the European Pharmacopoeia to detect the potential impurities should be demonstrated otherwise suitable validated methods and appropriate limits should be proposed.

Content of herbal drug (3.2.S.4)

Specification (3.2.S.4.1):

If specifications and test methods other than those described in the monograph concerned of the European Pharmacopoeia are used, they must be validated relative to the European Pharmacopoeia methods.

Any additional specifications shall be justified taking into account the *Note for guidance on specifications: test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products (CPMP/QWP/2820/00)*.

Analytical procedures (3.2.S.4.2):

This includes the description of controls applied to ensure the quality of the starting herbal drug used (botanical source, plant part used, geographical source, conditions of collection, and tests as described in the corresponding European Pharmacopoeia monograph for this herbal drug).

Validation of analytical procedures (3.2.S.4.3):

Analytical validation (if testing methods other than or supplementary to those of the European Pharmacopoeia are used) these are to be provided.

It may be possible to propose excluding certain tests of monograph on this basis, if justified.

Assay:



Assays of content of herbal drugs (constituents responsible of the therapeutic activity or marker compounds) are required in accordance with the European Pharmacopoeia monograph or by defaults with details of a suitable validated analytical procedure.

Batch analyses (3.2.S.4.4):

Results of testing of at least two batches will be given in order to evaluate the relevance of the monograph of the European Pharmacopoeia. When different methods of production or alternatives / different sites are described in the dossier, the results of the analysis of the batches shall be provided for each. The batch size and the date of production / and analysis will be given. The results of the analysis are given as actual figures whenever possible instead of statements such as “conforms”, “complies” etc.

The batch to batch variation should be discussed (impact of the geographical origin and climatic zone on the phytochemical profile).

In cases of use of TLC, a coloured photographic picture should illustrate the results.

Justification of specification (3.2.S.4.5):

Justification or additional specifications to those listed in the European Pharmacopoeia monograph will be provided.

Reference standards or materials (3.2.S.5)

Reference standard: if an European Pharmacopoeia CRS does not exist, the composition of the standard intended for use in assays should be adequately controlled and the purity of a standard should be measured by validated quantitative procedures.

Stability (3.2.S.7)

Due to the inherent complexity of herbal drugs 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.

Stability data should be assessed on the basis of the “Guideline on stability testing of existing active substances and related finished products (CPMP/QWP/556/96). The packaging material used and storage conditions will also figure on the certificate.

Quality Overall Summary (QOS)

A critical evaluation of the content of the dossier should be given in the form of a Quality Overall Summary (QOS)-(see The Rules Governing Medicinal Products in the European Community – Notice to Applicants for marketing authorizations for medicinal products for human use in the member states of the European Community, Volume II and addenda). It is expected that the Quality Overall Summary (QOS) should discuss the ability of the European Pharmacopoeia monograph to control the quality of the herbal drug, and in particular the declared potential impurities, or the necessity for alternative methods. Particular attention is given to justifying cases where testing for possible impurities are omitted, for example due to the fact that the impurity has not been detected in any batches or will not potentially be present due to a particular method of production.



Potential Toxicity of impurities

The applicant, if relevant, includes information on the potential toxicity of impurities either by reference to literature or by presentation of data to justify the proposed limits (see above, paragraph on *Impurities*).

HERBAL DRUG PREPARATION

The specific requirements listed in this section are in addition to those for the corresponding Herbal Drug.

General information (3.2.S.1)

Nomenclature (3.2.S.1.1):

The European Pharmacopoeia monograph name including the type of extract, the scientific botanical name according to the binomial system (genus, species, variety and author) and the common name if used for the labeling (together with the Ph.Eur.name), the part of the plant, the ratio herbal drug / herbal drug preparation, extraction solvent(s) should be stated together with any laboratory code used in the dossier.

Structure (3.2.S.1.2):

As per CTD

Manufacture (Production) / process (3.2.S.2)

Manufacturer (3.2.S.2.1):

The name and address of the intended producer(s) / manufacturer(s) and the proposed site(s) or facility(ies) involved in the production process should be provided. Other parties than the intended manufacturer(s) may be mentioned on the certificate when relevant: e.g. if other parties are involved in certain stages of the process; in this case details of their involvement and of other site addresses must be provided and information given on the contractual arrangements regarding sole or shared responsibilities. If an additional site is to provide alternative capacity batch analysis results for impurity profiles must be provided to demonstrate that the alternative arrangements yield preparation of the same quality as that produced by the first site.

Description of manufacturing process and Process Controls (3.2.S.2.2):

Information should be provided to adequately describe the manufacturing process of the herbal preparations, including:

- Description of the processing:
 - a) Brief outline flow chart, including the identification / characterization for the starting materials as described for “Herbal drug” and all intermediates.
 - b) Detailed description of each stage of manufacturing process of the herbal drug preparation (extraction, distillation, expression and purification), including information on preliminary treatment (inactivation of enzymes, grinding, or defatting),



- c) A maximum batch size should be stipulated, corresponding to batches already manufactured and referred to in the dossier.
- d) In case of alternative, extraction processes each of them should be clearly defined and described and not subject to addition of options.
- e) If a product with risk of transmitting agents of animal spongiform encephalopathies is used during the manufacture, the relevant monograph of the European Pharmacopoeia applies (Products with risk of transmitting agents of animal spongiform encephalopathies 1483),
- f) Description of controls applied to ensure the quality of any other starting material (solvents, reagents...,) excipients added during the production of the herbal drug / manufacture of the herbal drug preparation (including steps of extraction, distillation, expression, fractionation, purification, concentration or fermentation).
- Solvents, reagents
 - Purification stages: on intermediates and on herbal drug preparation
 - Standardisation: If preparations from herbal drugs with constituents of known therapeutic activity are standardised (i.e. adjusted to a defined content of constituent with known therapeutic activity) it must be stated how such standardisation is achieved. If another substance is used for these purposes, it is necessary to specify as a range the quantity that can be added. The compliance with the requirements of European Pharmacopoeia monograph should be given unless otherwise justified.

Characterisation (3.2.S.3)

Elucidation of the structure and other characteristics (3.2.S.3.1):

Information on the phyto- and physicochemical characterization, and biological activity if necessary should be provided.

Elucidation of the structure and other characteristics (3.2.S.3.2):

-All impurities originating from the starting material are to be controlled as described in the part related to herbal drug.

The following points should also be considered:

-Possible impurities originating from the process or from degradation should be listed and discussed with an indication of their origin.

The ability of the methods of the monograph of the European Pharmacopoeia to detect such impurities should be demonstrated otherwise suitable validated methods should be proposed.

-If alternative production / manufacturing processes are described the possible impurities are discussed separately for each route.

-Solvents

Where solvents are not covered by the general monograph for extracts, the prescriptions of the guideline for Residual Solvents prepared within the International Conference on Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) shall be applied (see 4.4).



Residual solvents, European Pharmacopoeia), i.e. the dossier shall demonstrate whether solvents have been used during the production / manufacturing process.

Toxic solvents (Class 1 and 2) should always be limited using a specific test, e.g. the test described in the general methods of the European Pharmacopoeia. As is indicated in the guideline class 1 solvents should not be employed in the production / manufacture of active substances or excipients unless there is a benefit/risk justification. Such justification should be provided. If class 2 solvents are used in the production / manufacturing process step prior to purification, the absence of such solvents in the final product should be demonstrated to justify the exemption of a test.

Non-toxic solvents (class 3) are also to be named and limited either using a specific test, or using a test for Loss on drying if the limit is not more than 0.5%.

Solvents to be controlled will be mentioned on the certification with the relevant test(s) and limit(s).

Note: Control of excipient (adjuvant, diluent, vehicle):

Excipients including those added during the manufacture of the herbal drug preparations should be described according to the Note for guidance on Excipients in the dossier for application for marketing authorization of a medicinal product (Volume 3A-Rules governing Medicinal products in the European Union for Human Medicinal Products, EMEA/CVMPM/004/98 for Veterinary Medicinal Products and controlled in Herbal Drug preparations according to the general / specific monographs.

Control of the herbal drug preparation (3.2.S.4)

Specification (3.2.S.4.1):

If specifications and test methods other than those described in the monograph concerned of the European Pharmacopoeia are used, they must be validated relative to the European Pharmacopoeia methods.

Any additional specifications shall be justified taking into account the Note for guidance on specifications: test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products (CPMP/QWP/2820/00).

Analytical procedures (3.2.S.4.2):

A description of controls applied to ensure the quality of the herbal drug preparation should be provided.

Validation of analytical procedures (3.2.S.4.3):

Analytical validation (if testing methods other than or supplementary to those of the European Pharmacopoeia are used), these are to be described.

It may be possible to propose excluding certain tests of the monograph on this basis if justified.

Assay:

Assays of content of herbal drug preparations (constituents responsible of the therapeutic activity or marker compounds) are required in accordance with the European Pharmacopoeia monograph or by defaults with details of a suitable validated analytical method.



Batch analysis (3.2.S.4.4):

Results of testing of at least two batches will be given in order to evaluate the relevance of the monograph of the European Pharmacopoeia. When different methods of production or alternatives / different sites are described in the dossier, the results of the analysis of the batches shall be provided for each. The batch size and the date of production and analysis will be given. The results of the analysis are given as actual figures whenever possible instead of statements such as “conforms”, “complies” etc.

In case of use of TLC, a coloured photographic picture should illustrate the results.

Justification of specification (3.2.S.4.5):

Justification of additional specifications to those listed in the European Pharmacopoeia monograph are to be provided.

Reference standards or materials (3.2.S.5)

Reference standard: if an European Pharmacopoeia CRS does not exist, the composition of the standard intended for use in assays should be adequately controlled and the purity of a standard should be measured by validated quantitative procedures.

Stability (3.2.S.7)

Due to the inherent complexity of herbal drug preparations 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 herbal drug preparation during its shelf life will be detected. Stability data should be assessed on the basis of the “Guideline on Stability testing of existing active substances and related finished products (CPMP/QWP/556/96). The packaging material used and storage conditions will also figure on the certificate.

Quality Overall Summary (QOS)

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Potential toxicity of impurities

The applicant, if relevant, includes information on the potential toxicity of impurities either by reference to literature or by presentation of data to justify the proposed limits (see above, paragraph on *Impurities*).