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Certification of suitability to Monographs of the European Pharmacopoeia

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

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

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I. INTRODUCTION

Herbal Drugs and Herbal drug preparations are defined in General monographs (1433) and (1434) of the European Pharmacopoeia (Ph. Eur.).

This document addresses the information to be provided for an application for a certificate of suitability as defined in Resolution AP-CSP (07) 1 of the Council of Europe⁽¹⁾.

This should be read in conjunction with the current version of the Ph. Eur. General monographs and General chapters identified by their respective numbers, and in conjunction with the EU Guidelines on the quality of herbal drugs and herbal drug preparations^(2,3,4). References to guidelines are given in the document to assist applicants and to provide useful information on the data expected in the respective sections. However, this reference list should not be regarded as comprehensive and the applicant should ensure that all relevant legislation and guidelines, as revised or maintained, are respected in the application when applicable.

II. Module 1 Administrative information: APPLICATION FORM

The Application Form – Request for New Certificate of Suitability, together with the relevant annexes, should be completed (it is available for download from the EDQM website, <http://www.edqm.eu>) and the appropriate declarations should be duly completed.

NB: Production should be conducted in accordance with the submitted dossier and with Good Manufacturing Practice (GMP) for starting materials. Official national and international guidelines should be adhered to, where applicable. Such guidance should be read in conjunction with the relevant guideline on Good Agricultural & Collection Practice (GACP)⁽⁵⁾. Other approaches to GMP of similar standards are acceptable, if justified⁽⁶⁾.

III. Module 2 : Quality Overall Summary (QOS)

A summary of the content of the dossier should be given in the form of a Quality Overall Summary (QOS)⁽⁷⁾. It is expected that the QOS should discuss the ability of the Ph. Eur. monograph to control the quality of the herbal drug or herbal drug preparation and, in particular, the declared potential impurities/contaminants or the necessity for alternative methods. Special attention is given to justifying cases where testing for possible impurities/contaminants are omitted due to the fact that the impurity / contaminant was not detected in batches from that origin or that the presence of the impurity / contaminant can be ruled out as a result of a particular production method".

The QOS should be signed and dated.

The CV of the expert that signs the QOS should be given, showing his/her experience in the field.

IV. Module 3 : DOCUMENTATION FOR HERBAL DRUG

Each section of the application should be presented in accordance with the numbering and terminologies of the CTD format^(7,8).

General information (3.2.S.1):

History of the product

Where applicable (if the product has been on the European market), the following data should be given: length of time the herbal drug has been produced in accordance with the application and included 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.

Nomenclature (3.2.S.1.1):

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

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 should be described. Parties other than the intended producer(s) may be involved and, in this case(s), details of their involvement and of other site addresses must be provided, together with information on the contractual arrangements regarding sole or shared responsibilities and demonstrated proof that any alternative production arrangements yield material of the same quality.

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

Information should be provided that adequately describes the plant production and plant collection, including:

- geographical source(s) 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):

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

Information should be provided on the botanical, macroscopic, microscopic and phytochemical characterisation, together with biological activity, if necessary.

This data should also include additional features that distinguish the herbal drug from potential adulterants and substitutes in case the monograph does not sufficiently cover this aspect.

Impurities (3.2.S.3.2):

Where applicable, possible impurities/contaminants originating from production and/or degradation should be listed, and their probable origin/cause should be discussed. If alternative production processes/sources are described, possible impurities/contaminants must be discussed separately for each process/route. This includes:

- Starting material = herbal material.
- Discrimination between related species, where relevant.
- Potential adulterants/substitutes/contaminants that are likely to be present.
- Foreign organic matter.
- Inorganic impurities/contaminants or toxic metals - the discussion should be based on the knowledge of the plant species, whether it is wild or cultivated and the production conditions.
- Pesticides, fumigation agents, *etc.*:
 - a) The potential for residues of pesticides should be considered taking into account whether the plant material is wild or cultivated and any treatments that the material is subjected to.
 - b) For fumigants, the relevant guidance should be used⁽⁹⁾.
- Radioactivity - this should be tested if there is cause for concern.
- Water content - this test is important when the herbal drug is known to be hygroscopic: Loss on drying procedure may be adequate. In some cases (plants containing essential oil) a detection procedure that is specific to water is required.
- Microbial contamination - a discussion on the need to determine the microbiological quality should be given. It should be based on the source of the herbal material and should take into account the inclusion of microorganisms specified in the Ph. Eur as well as other possible pathogens (e.g. *Campylobacter* and *Listeria species*).
- Mycotoxins (e.g. aflatoxins, ochratoxin A):- the potential for mycotoxins contamination should be fully considered.
- Degradation products - Where relevant, a description of potential degradation products should be given
- Potential toxicity of impurities/contaminants - if relevant, information on the potential toxicity of impurities/contaminants (either by reference to the literature or by presentation of data) should be given to justify the proposed limits.

Control of herbal drug (3.2.S.4):

Specification (3.2.S.4.1):

The specification of the herbal drug should be in compliance with the current general and specific Ph. Eur. monographs.

Where the monograph has been shown to not be suitable for controlling the quality of the herbal drug, additional analytical and validated methods should be presented in the dossier. Any tests additional to those of the monograph must be justified⁽²⁾.

It may also be possible to exclude some tests described in the monograph from the specification if they are not relevant for the control of the herbal drug. In such cases, this should be justified.

Impurities/contaminants

- Inorganic impurities/contaminants, toxic metals: The acceptance criteria described in the general Ph. Eur. monograph on Herbal drugs (1433) should be applied, unless otherwise justified. For other metals not listed in this monograph, it will ultimately depend on safety considerations. Where justified, specifications for sulfated ash, residue on ignition and heavy metals should be included and should follow pharmacopoeial requirements.
- Pesticides: The acceptance criteria of the Ph. Eur. general method (2.8.13) should be applied, unless otherwise fully justified. For potential residues not described in this chapter, acceptance criteria should be justified.
- Fumigation agents *etc.*: Acceptance criteria should be justified and should take into account the relevant legislation⁽⁹⁾.
- Microbial limits: The limits should comply with those of Ph. Eur. general chapter (5.1.8) and with current legislation⁽¹⁰⁾. Where appropriate, specifications for the total count of aerobic micro-organisms, the total count for yeasts and moulds and for the absence of specific objectionable bacteria should be defined.
- Mycotoxins (aflatoxins, ochratoxin A): For aflatoxins, the procedure and acceptance criteria should follow pharmacopoeial requirements (2.8.18) and, for ochratoxin A, the procedure should adhere to general chapter (2.8.22) and to the acceptance criteria given in specific monographs⁽¹⁰⁾.
- Degradation products: Where relevant, appropriate limits should be proposed.

Assay

- Assay: An assay for the content of the constituents with known therapeutic activity, active or analytical markers is required, in accordance with the specific Ph.Eur. monograph. NB: The selection of markers different to those described in the monograph should be strongly justified and indicative of stability⁽¹¹⁾.

European Pharmacopoeia monograph under revision

- If the specific Ph. Eur. monograph is in the process of being revised, the draft monograph may be taken into consideration by the producer and by the assessors if it provides useful information to test the quality of the herbal drug. However, application of the revised monograph is not mandatory before the implementation date.

Analytical procedures (3.2.S.4.2):

This section includes the tests described in the corresponding Ph. Eur. monograph for the herbal drug and the full description of any additional test methods applied to ensure the quality of the herbal drug.

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

Where test methods other than those described in the Ph. Eur. monograph are used, they must be validated against Ph. Eur. methods and the current regulatory requirements must also be taken into account⁽¹²⁾.

Impurities/contaminants:

Quantitative analysis of pesticide residues must be validated on the same or a comparable herbal matrix (according to the indications given in Ph. Eur. chapter 2.8.13).

For aflatoxins and ochratoxin A determination, the suitability of the methods of analysis (Ph. Eur. chapters 2.8.18 and 2.8.22, respectively) must be demonstrated on the same or a comparable herbal matrix.

For microbiological examination, the suitability of the method must be demonstrated according to Ph. Eur. chapter 2.6.31.

Where relevant, the suitability of the methods described in the monograph should be demonstrated or a suitably validated method should be developed.

Assay:

If the assay for the content of constituents with known therapeutic activity or for the active or analytical markers, is not done in accordance with the relevant Ph. Eur. monograph, a suitable alternative analytical method that is fully validated should be proposed⁽¹²⁾.

Batch analysis (3.2.S.4.4):

The results of testing at least two batches of the herbal drug should be given in order to evaluate the relevance of the Ph. Eur. monograph and the quality of the product. When different methods of production or alternative/different sites are described in the dossier, the results of analyses must be provided for each production method/site.

The batch size and the dates of production and analyses should be given. The results of analyses should include actual figures whenever possible, instead of statements such as "conforms", "complies", *etc.* Where thin-layer chromatography (TLC) is used, a coloured photographic picture should illustrate the results.

Batch-to-batch variation should be discussed (*e.g.* impact of the geographical origin and climatic zone on the phytochemical profile).

Justification of specification (3.2.S.4.5):

In this section, the suitability of the specific monograph to control the quality of the herbal drug has to be demonstrated, and the justification for tests additional to those listed in the monograph should be provided.

It may be possible to propose an exclusion of some tests described in the monograph if they are not relevant for the control of the product and if appropriately justified.

Reference standards or materials (3.2.S.5):

If a suitable Ph. Eur. chemical reference standard (CRS) or Ph. Eur. herbal reference standard (HRS) does not exist, the composition of the standard intended for use in assays should be adequately controlled and the purity of the standard should be measured by validated quantitative procedures (see Ph. Eur. chapter 5.12 on reference standards).

Container closure system (3.2.S.6):

The container closure system should be described and should include a description and identification of materials for each primary packaging component. A specification for each of these components should be supplied. Where relevant, conformity to current regulations on plastic packaging should be demonstrated^(13,14). The suitability for use of the container closure system should be discussed and, if applicable, this should be linked to the storage recommendations of the specific Ph. Eur. monograph.

Stability (3.2.S.7):

When a re-test period is requested by the applicant, stability information from at least two batches of the herbal drug should be submitted. The types of studies conducted on the herbal drug, the protocols used and the results of the studies should be described^(3,10,11,15,16). The summary should include conclusions with respect to storage conditions and the re-test date of the product.

A description of batches (*i.e.* batch size, date of production) should be provided, as well as details of the packaging material used for stability studies.

Due to the inherent complexity of herbal drugs, there may be no single stability-indicating assay or parameter that adequately profiles the stability characteristics. Consequently, the applicant should propose a series of product-specific, stability-indicating tests, the results of which provide assurances that changes in the quality of the product during storage are detected.

Stability results should be presented in an appropriate format (tabular, graphic or narrative). Chromatographic profiles demonstrating that the chromatogram fingerprints remain comparable to the initial fingerprint should be provided. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

In the absence of stability studies, a herbal drug that is used as a starting material in the manufacturing process for a herbal drug preparation must comply with the specification immediately before use (*i.e.* before extraction).

V. Module 3: DOCUMENTATION FOR HERBAL DRUG PREPARATION

When submitting an application for a herbal drug preparation, the requirements listed in this section are provided in addition to those for the corresponding herbal drug.

The quality of the herbal drug preparation should meet the requirements-including the Definition and Production sections- of the specific relevant Ph. Eur. monograph.

General information (3.2.S.1):

History of the product

Where applicable (if the product has been on the European market), the following data should be given: length of time the herbal drug preparation has been produced in accordance with the application and included 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.

Nomenclature (3.2.S.1.1):

The following should be described:

- the Ph. Eur. monograph name including the type of extract, the scientific botanical name according to the binominal system (genus, species, variety and author) and the common name if used for the labelling (together with the Ph. Eur.name).
- the part of the plant.
- the ratio of herbal drug / herbal drug preparation (DER native extract (genuine) and DER finished extract).
- the extraction solvent(s), including the strength of each solvent.
- where applicable, the name of the excipients added to adjust the content of constituents with known therapeutic activity, the excipients added for technological reasons (fixed percentage or defined narrow percentage range), stabilisers, antioxidants, antimicrobial preservatives,
- any laboratory code used in the dossier.

Manufacture (Production) (3.2.S.2):

Manufacturer (3.2.S.2.1):

The name(s) and address(es) of the intended producer(s)/manufacturer(s) and the proposed site(s) or facility(ies) involved in the production should be provided. Parties other than the intended producer(s) may be involved and, in this case, details of their involvement and of other site addresses must be provided, together with information on the contractual arrangements regarding sole or shared responsibilities and demonstrated proof that the alternative arrangements yield preparations of the same quality.

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

Where the monograph includes a production section, fulfillment of the requirements of this section should be discussed in the application.

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

- Description of the processing stages:

- Brief outline flow chart, starting from introduction of the herbal drug used as starting material and covering all further steps including intermediates.
- Detailed description of each stage of the manufacturing process of the herbal drug preparation (extraction, distillation, expression, fractionation, purification concentration or fermentation), including information on preliminary treatment (inactivation of enzymes, grinding or defatting) and microbial decontamination treatment. Critical steps should be mentioned and discussed (duration of extraction, temperature, *etc.*).
- A maximum batch size should be stipulated, corresponding to batches already manufactured and referred to in the dossier.
- In case of alternative extraction processes, each of these should be clearly defined and described and shown to be equivalent, i.e. resulting in a herbal preparation of equal quality and complying with the same specification.
- If a product with a risk of transmitting agents of animal spongiform encephalopathies (TSE) is used during manufacture, the relevant Ph. Eur. monograph applies (*Products with risk of transmitting agents of animal spongiform encephalopathies, 1483*).

- Solvents, reagents:

Materials used in the manufacture of the herbal drug preparation should be listed, identifying the stage at which each material is used in the process.

- Purification stages:

All purification steps performed on the intermediates and on the herbal drug preparation should be described in the application.

- 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 an excipient is used for these purposes, it is necessary to specify (as a range) the quantity that can be added.

Control of materials (3.2.S.2.3):

Information on the quality and control of materials used in the manufacture of the herbal drug preparation should be provided and that such materials meet the appropriate standards for their intended use.

Herbal drug (3.2.S.2.3.1):

Information about the herbal drug should be given, and should comply with the requirements described in Section IV of this document. It may be possible to propose excluding certain tests, if appropriately justified.

Batch results from at least two batches of the herbal drug should be submitted.

Solvents (3.2.S.2.3.2):

Appropriate specifications for solvents should be supplied.

Where organic solvents are recovered from the preparation of the extract or recycled, this is acceptable provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate and justified standards before re-use or mixture with other approved materials. The procedure should be described in the application.

Water used for the manufacture of extracts should comply with the Ph. Eur. monograph *Water for Preparation of Extracts (2249)*.

Excipients (3.2.S.2.3.3):

All excipients (e.g. excipients added for technological reasons, excipients added for adjustment reasons, antioxidants...) added during the manufacture of the herbal drug preparation should be described^(3,17).

Excipients are controlled in the herbal drug preparation according to the general/specific monographs.

If novel excipients are used, the dossier requirements for active substances apply⁽¹⁸⁾.

Controls of critical steps and intermediates (3.2.S.2.4):

Any critical steps should be identified, and in-process tests and acceptance criteria should be described. Information on the quality and control of intermediates isolated during manufacture should be provided.

Characterisation (3.2.S.3):

Impurities (3.2.S.3.2):

For all impurities/contaminants originating from the herbal drug, reference should be made to the impurities/contaminants section relating to herbal drug:

Where applicable and depending on the quality, impurity profile and tests carried out on the herbal drug used for the manufacture (and considering the manufacturing process, *i.e.* possible decrease or concentration of impurities/contaminants), a discussion on the necessity to include tests for microbiological quality, heavy metals, aflatoxins, ochratoxin A and pesticide residues in the extracts should be given.

The following impurities/contaminants should also be considered:

- Possible impurities/contaminants originating from the process, from solvents or from degradation should be listed and discussed with an indication of their origin.
- The solvents used during the production process (from extraction to purification) and their ICH classification should be listed.

As is indicated in the related ICH guideline⁽¹⁹⁾, Class 1 solvents should not be employed unless there is a risk/benefit justification, which should be described in full. The final decision on the acceptability of the use of a Class 1 solvent is taken by the Certification Technical Advisory Board.

If alternative production/manufacturing processes are described, the possible impurities/contaminants must be discussed separately for each process.

Potential toxicity of impurities/contaminants:

If relevant, the applicant should include information on the potential toxicity of impurities/contaminants, either by reference to the literature or by presentation of data to justify the proposed limits.

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

Specification (3.2.S.4.1):

The specification of the herbal drug preparation should include the tests of the specific Ph. Eur. monograph, as well as any necessary additional tests to control the quality and purity.

Any additional tests must be justified⁽²⁾ and should be in line with current regulatory requirements. Where a test for heavy metals is necessary, the same limits for heavy metals as those given in the Ph. Eur. general monograph on Herbal Drugs (1433) are applicable for extracts unless otherwise stated in the individual extract monograph or unless otherwise justified⁽¹⁰⁾.

Impurities

Where solvents are not covered by the general Ph. Eur. monograph for Extracts (0765), these should be controlled as described in Ph. Eur. general chapter 5.4⁽¹⁹⁾. In addition, Annex 1⁽²⁰⁾ of the *Guideline for Residual Solvents*⁽²¹⁾ should be taken into consideration when setting specifications. Toxic solvents (Class 1 and 2) should always be limited using a specific test, e.g. the test described in Ph. Eur. general method 2.4.24.

If Class 2 solvents are used in the steps 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) must also 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 per cent. If the limit exceeds 0.5 per cent, method of analysis 2.4.24 must be applied.

Assay:

An assay of the content of the constituents responsible for therapeutic activity or active or analytical markers should be in compliance with the Ph. Eur. monograph.⁽¹¹⁾ NB: The selection of markers different to those described in the monograph should be strongly justified and indicative of stability⁽¹¹⁾.

Analytical procedures (3.2.S.4.2):

This section includes the tests as described in the corresponding Ph. Eur. monograph for the herbal drug preparation and the description of the additional controls applied to ensure the quality of the herbal drug preparation.

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

If test methods other than those described in the Ph. Eur. monograph are used, they must be validated against Ph. Eur. methods and should be in line with the requirements of the current version of the Ph. Eur. general monograph on Extracts (0765). It may be possible to propose excluding certain tests of the monograph on this basis if a justified rationale is provided.

Where relevant, the suitability of the methods of the monograph should be demonstrated or an appropriate validated method should be developed.

Assay:

For herbal drug preparations, the assay of the content of the constituents with known therapeutic activity or active or analytical markers should be in compliance with the corresponding individual Ph. Eur. monograph or another appropriate assay method may be used, provided that the analytical method is validated and validation data is submitted⁽¹²⁾.

Batch analysis (3.2.S.4.4):

The test results of at least two batches of the herbal drug preparation should be given in order to evaluate the relevance of the Ph. Eur. monograph and the quality of the product. When different methods of manufacture or alternatives/different sites are described in the dossier, the results of analyses must be provided for each production/site.

The batch size and the dates of manufacture and analyses should be given. The results of the analyses should include actual figures whenever possible, instead of statements such as "conforms", "complies", *etc.* Where thin-layer chromatography (TLC) is used, a coloured photographic picture should illustrate the results.

Justification of specification (3.2.S.4.5):

In this section, the suitability of the specific monograph to control the quality of the herbal drug preparation has to be demonstrated, and a justification of additional tests to those listed in the monograph should be provided.

It may be possible to propose exclusion of some tests of the monograph if they are not relevant for the control of the product and if they are appropriately justified.

Reference standards or materials (3.2.S.5):

If a suitable Ph. Eur. chemical reference standard (CRS) or Ph. Eur. herbal reference standard (HRS) does not exist, the composition of the standard intended for use in the assay should be adequately controlled and the purity of the standard should be measured by validated quantitative procedures.

Container Closure System (3.2.S.6):

The container closure system should be described and should include a description and identification of materials of construction for each primary packaging component. The specification of these components should be supplied. Where relevant, conformity to current regulations on plastic packaging should be demonstrated^(13,14). The suitability for use of the container closure system should be discussed and, if applicable, this should be linked to the storage recommendations of the specific Ph. Eur. monograph.

Stability (3.2.S.7):

When a re-test period is requested by the applicant, stability information from at least two batches of the herbal drug preparation should be submitted. The types of studies conducted on the product, the protocols used and the results of the studies should be described^(3,10,11,15,16). The summary should include conclusions with respect to storage conditions and the re-test period, as appropriate. Stress testing is usually considered unnecessary for herbal preparations.

Reminder: In the absence of stability studies, a herbal drug that is used as a starting material in the manufacturing process for a herbal drug preparation must comply with its specification immediately before use (*i.e.* before extraction).

A description of the batches put in stability (batch size, date of manufacture) should be provided, as well as details of the packaging material used for stability studies.

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 provide assurances that changes in the quality of the product during storage are detected.

Stability results should be presented in an appropriate format (tabular, graphic or narrative). Chromatographic profiles demonstrating that the chromatogram fingerprints remain comparable to the initial fingerprint should be provided. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

VI. References

(1) Resolution AP-CSP (07) 1 of the Council of Europe, Certification of suitability to the monographs of the European Pharmacopoeia (revised version).

(2) Guideline on specifications: test procedures and acceptance criteria for herbal substances ^(a), herbal preparations ^(b) and herbal medicinal products/traditional herbal medicinal products^(c) (CPMP/QWP/2820/00; EMEA/CVMP/815/00).

NB: ^a *The term "herbal substance" should be considered as equivalent to the term "herbal drug" as defined in the European Pharmacopoeia*

^b*The term "herbal preparation" should be considered as equivalent to the term "herbal drug preparation" as defined in the European Pharmacopoeia*

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

(3) Guideline on quality of herbal medicinal products (CPMP/QWP/2819/00; EMEA/CVMP/814/00).

(4) Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products (EMA /HMPC /CHMP /CVMP /287539 /2005).

(5) Guideline on Good Agricultural and Collection Practice (GACP) for starting material of herbal origin (EMEA/HMPC/246816/2005).

(6) Volume 4 of EU Guidelines to Good Manufacturing Practice: Medicinal products for human and veterinary use Part II and Annex 7 Manufacture of Herbal Medicinal Products.

(7) Notice to Applicants, Volume 2B: Presentation and content of the dossier (CTD), module 2.

(8) Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products (EMEA/HMPC/71049/2007).

(9) Reflection paper on the use of fumigants (EMEA/HMPC/125562/2006).

(10) Questions & Answers on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products - EMA/HMPC/41500/10).

(11) Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products (EMEA/HMPC/253629/2007).

(12) Note for Guidance on validation of analytical procedures: text and methodology (CPMP/ICH/381/95).

(13) Guideline on plastic immediate packaging materials (CPMP/QWP/4359/03).

(14) Commission Directive (2002/72/EC) relating to plastic materials and articles intended to come into contact with foodstuffs.

- (15)** Guideline on stability testing of existing active substances and related finished products (CPMP/QWP/122/02).
- (16)** Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products (EMA/HMPC/3626/2009).
- (17)** Guideline on excipients in the dossier for application for marketing authorization of medicinal products (EMA/CHMP/QWP/396951/06).
- (18)** Directive 2001/83/EC as amended for human medicinal products and Directive 2001/82/EC as amended for veterinary medicinal products).
- (19)** ICH Q3C; Impurities: Guideline for Residual Solvents (CPMP/ICH/283/95) and General Chapter 5.4 of the European Pharmacopoeia on Residual solvents.
- (20)** Annex I to CPMP/ICH/283/95 Impurities: Guideline for Residual Solvents and CVMP/VICH/502/99 Guideline on Impurities: Residual Solvents: Specifications for Class 1 and Class 2 residual solvents in active substances (CPMP/QWP/450/03, EMA/CVMP/511/03).