The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS

Final Comments for Revision of the Notice to Applicants Volume 2B Part II: Concerning Chemical, Pharmaceutical and Biological Documentation for Vegetable Medicinal Products

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Final Comments for revision of Notice to Applicants Volume 2B Part II: Concerning chemical, pharmaceutical and biological documentation for vegetable medicinal products - (EMEA/HMPWG/8/99)

The ad hoc Working Group on Herbal Medicinal Products suggests amending the text as follows. Changes are in bold italic.

Part II: Concerning Chemical, Pharmaceutical and Biological Documentation for *Herbal* Medicinal Products

The principle of GMP and the detailed guidelines are applicable to all operations, which require the authorisation referred to in **Article 16 of Directive 75/319/EEC** as modified. They are also relevant for all other large-scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, for the preparations of products for use in clinical trials, and for wholesaling, where applicable.

All analytical test procedures described in the various sections of the Part II chemical, pharmaceutical and biological documentation must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.

PART II A: COMPOSITION

1. COMPOSITION OF THE MEDICINAL PRODUCT

NAMES OF INGREDIENTS	UNIT AND/OR PERCENTAGE FORMULA	FUNCTION	REFERENCE TO STANDARDS
Active substance(s)			
Excipient(s)			

2. CONTAINER (BRIEF DESCRIPTION)

Nature of container materials; qualitative composition; method of closure; method of opening.

3. CLINICAL TRIAL FORMULA(E)

4. *DOSAGE FORM* - DEVELOPMENT PHARMACEUTICS

Explanation with regard to the choice of formulation, composition, ingredients and container, supported, if necessary, by data on development pharmaceutics. The overage, with justification thereof, should be stated. Tests carried out during pharmaceutical development must be described in detail, e. g. in vitro dissolution studies for solid pharmaceutical forms.

PART II B: METHOD OF PREPARATION

1. MANUFACTURING FORMULA (including details of batch size)

2. MANUFACTURING PROCESS (including in-process control and the pharmaceutical assembly process)

If ***herbal drug*** preparations are the starting material, the description of their manufacturing process and their control belong to section C.
A flow-chart of the manufacturing process should be given.

3. VALIDATION OF THE PROCESS

Validation of the process should be carried out when a non-standard method of manufacture is used or for steps of the manufacturing process which are critical for the product described in the finished product specifications (experimental data showing that the manufacturing process, using materials of the stated quality and the types of manufacturing equipment specified, is a suitable one and will consistently yield a product of the desired quality).

PART II C: CONTROL OF STARTING MATERIALS

1. ACTIVE SUBSTANCE(S) ***(HERBAL DRUG(S)/(HERBAL DRUG PREPARATION(S))***

1.1. Specifications and routine tests

1.1.1 Active substance(s) described in a pharmacopoeia
For herbal drug preparations additional specifications as set out in 1.1.2 may be required.

1.1.2 Active substance(s) not described in a pharmacopoeia

- Characteristics
- Identification tests
- ***Purity tests***
  * Potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactivity, fumigants, etc.
  * Physical
  * Chemical
- Other tests
- Assay(s) of ***constituents*** with known therapeutic activity ***or of markers, or other justified determination***.

In the case of a herbal drug preparation, a monograph on the herbal drug has to be presented. If no monograph for the herbal drug exists, neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, a comprehensive specification of the herbal drug has to be presented.

1.2. Scientific Data

1.2.1 Nomenclature

- Scientific name of plant, with the name of the authority, variety and chemotype ***(where applicable)***
- ***Parts of the plant***

- ***Definition of the herbal drug/herbal drug preparation***
- ***Ratio of the herbal drug to the herbal drug preparation***
- ***Extraction solvent(s)***
- Other name
- Laboratory code

1.2.2 Description

- Physical form
- ***Constituents with known therapeutic activity or markers***
  - · Structural formula (including conformational data for macromolecules)
  - · Molecular formula
  - · Relative molecular mass
  - · Chirality
- ***Other substance(s)***

1.2.3 Manufacture

- ***Definition of a production batch***
- ***Plant production/Plant collection***
- Geographical source of active substance ***of herbal origin***
- Name(s) and address(es) of the ***manufacturer of the preparation***
- ***Manufacturing route***
- Description of process
- Solvents, reagents
- Purification stages
- ***Standardisation***

1.2.4 Quality control during manufacture

- Starting materials
- Control tests on intermediate products (where appropriate)

1.2.5 Development (for active substance(s) of ***herbal*** origin)

1.2.5.1 ***Herbal drugs, herbal drug preparations such as powders***

- Description of the ***herbal drug or of the herbal drug preparation***
  - macroscopic
  - microscopic
  - ***Additional tests***
- Composition and analytical research for ***constituents*** and physical characteristics
- ***Tests for adulterants and for known toxic constituents***
- ***Summary of*** analytical development and validation ***studies***, commentary on the choice of routine tests and specifications

1.2.5.2 ***Herbal drug preparations such as extracts***

- Analytical chemical profile (qualitative and quantitative)
- Detection of ***known*** toxic ***constituents (e.g. pyrrolizidine alkaloids, ginkgolic acids, estragole, thujone, ...)*** /adulterants
- ***Summary of*** analytical development and validation ***studies***, commentary on the choice of routine tests and specifications.

1.2.6 Impurities

- Potential impurities originating from the ***cultivation, harvesting/collection, storage***
- Potential impurities arising during the production and purification, ***residual solvents***
- Methods detecting potential contamination of the active substance(s) ***of herbal origin*** by micro-organisms and products of micro-organisms, pesticides, fumigation agents, toxic metals, radioactivity etc.
- Potential ***substitution and adulterants***

1.2.7 Batch analysis

- Batches tested (date of manufacture, place of manufacture, batch size, and use of batches including batches used in preclinical and clinical testing)
- Results of tests
- Reference ***standard*** (analytical results), primary and others

2. EXCIPIENT(S)

2.1. Specifications and routine tests

2.1.1 Excipient(s) described in a pharmacopoeia

2.1.2 Excipient(s) not described in a pharmacopoeia

- Characteristics
- Identification tests
- Purity tests (including limits for named, total, other single, unidentified single and unidentified total impurities)
  - physical
  - chemical
  - ***biological/immunological***
- Other tests
- Assay(s) and/or evaluations (where necessary)

2.2. Scientific data

Data, where necessary, for example on excipient(s) used for the first time in medicinal products (see II C.1.2).

3. PACKAGING MATERIAL (IMMEDIATE PACKAGING)

3.1 Specifications and routine tests

- Type of material
- Construction
- Quality specifications (routine tests and ***summary of control methods***)

3.2 Scientific data

- Development studies on packaging materials
- Batch analysis, analytical results

PART II D: CONTROL TESTS ON INTERMEDIATE PRODUCTS (IF NECESSARY)

A distinction should be made between in-process controls (Part II B) and control tests on intermediate products.

PART II E: CONTROL TESTS ON THE FINISHED PRODUCT

1. SPECIFICATIONS AND ROUTINE TESTS

1.1 Product specifications and tests for release at time of manufacture (general characteristics, specific standards)

1.2 Control Methods

1.2.1 Test procedures for identification and quantitative determination ***of herbal drugs/herbal drug preparations.***

It must be described in detail (including biological and micro-biological methods where relevant), together with other tests which include those in the appropriate general monograph for the type of dosage form in the European Pharmacopoeia:

- Identification tests
- Quantitative determination of active substance(s); and additionally for ***herbal drugs*** and ***herbal drug preparations***, quantitative determination of ***constituents*** with known therapeutic activity ***or of markers, or other justified determination***
- Purity tests
- Pharmaceutical tests (e.g. dissolution)

1.2.2 Identification and determination of excipient(s)

- Identification tests for approved colouring materials
- Determination of ***preservative agents, e.g.*** antimicrobial or chemical preservatives (with limits)
- ***Other additives***

2. SCIENTIFIC DATA

2.1 Analytical validation of methods and comments on the choice of routine tests and standards (e.g. working standards)

2.2 Batch analysis

- Batches tested (date of manufacture, place of manufacture, batch size and use of batches)
- Results of ***batch analysis***
- Reference ***standard*** (analytical results), primary and others

PART II F: STABILITY

1. STABILITY TESTS ON ACTIVE SUBSTANCE(S)

- Batches tested
- General test methodology
  - accelerated test conditions
  - normal test conditions
- Analytical test procedures
  - assay ***techniques***
  - determination of degradation products/***chromatographic profile***
- Validation of all test procedures including limits of detection (including initial results)
- Results of tests
- Conclusions

Data on stability tests on active substances may not be required if justified by the applicant, provided that the finished product is manufactured immediately after production of the active substance(s).

2. STABILITY TESTS ON THE FINISHED PRODUCT

- Quality specification for the proposed shelf-life
- Batches tested and packaging
- ***Stability*** study methods
  - real time studies
  - studies under other conditions
- Characteristics studied
  - physical characteristics
  - microbiological characteristics
  - chemical characteristics
  - chromatographic characteristics
  - characteristics of the packaging (container/closure interaction with the product)
- Evaluation test procedures
  - description of test procedures
  - validation of test procedures
- Results of tests (including initials and reference to degradation products)
- Conclusions
  - shelf-life and storage conditions
  - shelf-life after reconstitution or first opening of the product
- Ongoing stability studies

PART II G: BIOAVAILABILITY/ BIOEQUIVALENCE

Give reference to relevant sections in Part IV.

PART II Q: OTHER INFORMATION

This part is intended for information not covered by any of the previous parts, e.g. the analytical tests used for the pharmaceutical development of the product, studies concerning metabolism and bioavailability, etc.