PART II

X. CONCERNING CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL DOCUMENTATION FOR VEGETABLE MEDICINAL PRODUCTS

The principle of GMP and the detailed guidelines are applicable to all operations which require the authorization 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 preparation of products for use in clinical trials, and for wholesaling, were 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

<table>
<thead>
<tr>
<th>NAMES OF INGREDIENTS</th>
<th>UNIT AND/OR PERCENTAGE FORMULA</th>
<th>FUNCTION</th>
<th>REFERENCE TO STANDARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance(s)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Excipient(s)</td>
<td></td>
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</tr>
</tbody>
</table>

2 CONTAINER (BRIEF DESCRIPTION)
Nature of container materials; qualitative composition; method of closure; method of opening.

3 CLINICAL TRIAL FORMULA(E)

4 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.

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53 see the annex, reference 61
54 see the annex, reference 9
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 vegetable active substance preparations are the starting material, the description of their manufacturing process and their control belong to section C.

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)
1.1. Specifications and routine tests
1.1.1 Active substance(s) described in a pharmacopoeia
1.1.2 Active substance(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
  * Potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactivity, fumigants, etc.
- Other tests
- Assay(s) of excipients of vegetable active substances or vegetable active substance preparations with known therapeutic activity
- In the case of vegetable active substance preparations, a monograph on the vegetable active substance
1.2. Scientific Data

1.2.1 Nomenclature
- International non-proprietary name (INN)
- Chemical name
- Other name
- Laboratory code
- In the case of vegetable active substance(s)
  - Scientific name of plant, with the name of the authority, variety and chemotype
  - Parts employed of the herb
  - Name of the preparation

1.2.2 Description
- Physical form
- Structural formula (including conformational data for macromolecules)
- Molecular formula
- Relative molecular mass
- Chirality
- Main excipients of vegetable active substances based on recent scientific data

1.2.3 Manufacture
- Name(s) and address(es) of the manufacturing source(s)
- Geographic source of vegetable active substance.
- Synthetic or manufacturing route
- Description of process
- Solvents, reagents; excipients
- Catalysts
- Purification stages

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 vegetable origin)

1.2.5.1 Vegetable active substance
- Description of the vegetable active substance(s)
  - macroscopic
  - microscopic
- Composition and analytical research for excipients and physical characteristics
- Investigation for adulterants of known toxic excipients
- Analytical development and validation, commentary on the choice of routine tests and specifications

1.2.5.2 Vegetable active substance preparation (e.g. powder extract)
- Analytical chemical profile (qualitative and quantitative)
- Detection of toxic excipients/adulterants
- Analytical development and validation, commentary on the choice of routine tests and specifications.
1.2.6 Impurities
- Potential impurities originating from the route of synthesis
- Potential impurities arising during the production and purification
- Methods detecting potential contamination of the vegetable active substance(s) by micro-organisms and products of micro-organisms, pesticides, fumigation agents, toxic metals, radioactivity etc.
- Potential falsification and adulterants of the vegetable active substance(s)

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 material (analytical results), primary and others

2 EXCIPIENTS

2.1 Specifications and routine tests
2.1.1 Excipients described in a pharmacopoeia
2.2.2 Excipients 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
- 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 test procedures

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 for the active substance(s).

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 vegetable active substances and vegetable active substances preparation, quantitative determination of excipients with known therapeutic activity
- Purity tests
- Pharmaceutical tests (e.g. dissolution)

1.2.2 Identification and determination of excipient(s)

- Identification tests for approved colouring materials
- Determination of antimicrobial or chemical preservatives (with limits)

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 obtained
- Reference material (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
  - determination of degradation products
- Validation of all test procedures including limits of detection (including initial results)
- Results of tests
- Conclusions

2 STABILITY TESTS ON THE FINISHED PRODUCT
- Quality specification for the proposed shelf-life
- Batches tested and packaging
- 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 and/or first opening of the product
- Ongoing stability studies

PART II G: BIOAVAILABILITY/BIOEQUIVALENCE

Give reference to relevant sections in Part IV.

PART II H: DATA RELATED TO THE ENVIRONMENTAL RISK ASSESSMENT FOR PRODUCTS CONTAINING/CONSISTING OF GENETICALLY MODIFIED ORGANISMS (GMOS)

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.