QUALITY OF HERBAL MEDICINAL PRODUCTS: PRESENT REQUIREMENTS

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CONTENTS

- Production of herbal starting materials, active substances and medicinal products
- Requirements of the Pharmacopoeia
- Particularities of the quality dossier and in marketing authorisation/registration: legal requirements, Common Technical Document (CTD), Guidance documents
GMP AND QUALITY ASSURANCE SYSTEM

- Commission **Directive 2003/94/EC** of 8 October 2003 laying down the principles and guidelines of **Good Manufacturing Practice** ...
- **Article 6**: „The manufacturer shall establish and implement an effective pharmaceutical Quality Assurance (QA) System ...“
GMP AND QUALITY ASSURANCE SYSTEM

- Detailed guidance with reference to Directive 2003/94/EC: EU GMP Guideline
- Part I: Production of medicinal products
- Part II: „Basic Requirements for Active Substances used as Starting Materials“
- Special Annexes e.g. Annex 7 on the manufacture of herbal medicinal products (incl. active substances)
## ANNEX 7: APPLICABILITY OF GMP

<table>
<thead>
<tr>
<th>Activity</th>
<th>Good Agricultural and Collection Practice</th>
<th>Part II of the GMP Guide</th>
<th>Part I of the GMP Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection, Cultivation and harvesting of plants, algae, fungi and lichens, and collection of exudates</td>
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<td>Cutting and drying of plants, algae, fungi, lichens and exudates</td>
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<td>Expression from plants and Distillation</td>
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<td>Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances substances</td>
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<td>Further processing into a dosage form including packaging as a medicinal product</td>
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ANNEX 7 TO EU GMP GUIDELINE

- Various footnotes e.g.
- GMP classification depends on the intended use of the material (e.g. herbal drug for extraction or as tea/ final product)
- E.g. cutting or drying ”in the field”: GACP Standards applicable; GMP for further production steps
GACP: GOOD AGRICULTURAL AND COLLECTION PRACTICE

- 1998 – 2002 developed by Europam, EMA, WHO
- 2006: EMA Guideline (HMPC)
- Useful recommendation "to fill the gap" for active substances of herbal origin in case GMP rules are not directly applicable
- Content: e.g. seed and propagation material, cultivation and collection, irrigation, fertilisation, pest management/plant protection products, harvesting, drying and further processing
GACP: GOOD AGRICULTURAL AND COLLECTION PRACTICE

- Part of the QA System of the manufacturer in order to guarantee a high and consistent quality
- Viewpoint of cultivators and herbal industry:
- Pragmatic handling of initial process steps for e.g. herbal teas, extracts, tinctures, essential oils:
THE EUROPEAN PHARMACOPOEIA (PH.EUR.)

Source: EDQM
## THE EUROPEAN PHARMACOPOEIA (PH.EUR.)

<table>
<thead>
<tr>
<th>Commission Sessions</th>
<th>8th Edition Supplements</th>
<th>Publication Schedule</th>
<th>Implementation Date</th>
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BASIC REQUIREMENTS FOR MARKETING AUTHORISATION/REGISTRATION OF HERBAL MEDICINAL PRODUCTS

European Pharmacopoeia monograph „Herbal drug extracts“

- Completely revised and published … together with a detailed explanatory chapter (5.23)
- All individual monographs on herbal extracts to be read in conjunction with the general chapter „herbal extracts“
- Definition: „…liquid (liquid extracts and tinctures), semi-solid (soft extracts and oleoresins) or solid (dry extracts) preparations ..., obtained from herbal drugs … using suitable solvents.“
European Pharmacopoeia monograph
„Herbal drug extracts“

- Monograph covers genuine extracts plus excipients (in accordance with the market)
- Requirements for the use of excipients as well as for the use of recovered solvents (e.g. control and monitoring of recovery procedures, appropriate standards to be met)
- Tests depending on preparation e.g. density, ethanol content; loss on drying/ water content
- Labelling
European Pharmacopoeia monograph
„Herbal drug extracts“
- Particular requirements for different preparations (dry extracts, liquid extracts, oleoresins ..)
- Types of extracts: standardised, quantified and „other“ extracts (depending on the occurrence of constituents with known therapeutic efficacy)
- Glossary with explanation of terms
## MONOGRAFIE „EXTRAKTE“

<table>
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<tr>
<th>Type of extract</th>
<th>Relevance</th>
<th>Marker</th>
<th>Native extract</th>
<th>Blending</th>
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</thead>
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<tr>
<td>Standardized</td>
<td>Constituents with known therapeutic activity</td>
<td>Active substance (constant)</td>
<td>Variable</td>
<td>With inert material or by blending of batches</td>
</tr>
<tr>
<td>Quantified</td>
<td>Extract is active subst. (active marker contributes to therapeutic efficacy)</td>
<td>Active marker (constant, but range)</td>
<td>Constant</td>
<td>By blending of batches</td>
</tr>
<tr>
<td>„Other“</td>
<td>Extract is active substance</td>
<td>Analytical marker (variable)</td>
<td>Constant</td>
<td>./</td>
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</tbody>
</table>
BASIC REQUIREMENTS FOR MARKETING AUTHORISATION/REGISTRATION OF HERBAL MEDICINAL PRODUCTS

- Quality
- Safety
- Efficacy

Manufacturer/Applicant

National health authority, e.g. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
BASIC REQUIREMENTS FOR MARKETING AUTHORISATION/REGISTRATION OF HERBAL MEDICINAL PRODUCTS

- **Marketing authorisation:**
  Efficacy and safety based on own pharmacological/toxicological/clinical data or bibliographic references (published pharmacological/toxicological/clinical data)

- **Registration:**
  Traditional use based on at least 30 years experience and plausible effects/efficacy

- Reference to HMPC monographs possible

- Complete quality documentation required in all cases
Quality dossier  
(Module 3 according to Annex I to Directive 2001/83/EC)

3.2.1. Active substance (s)
3.2.1.1. General information and information related to the starting and raw materials
3.2.1.2. Manufacturing process of the active substance (s)
3.2.1.3. Characterisation of the active substance (s)
3.2.1.4. Control of active substance (s)
3.2.1.5. Reference standards or materials
3.2.1.6. Container and closure system of the active substance
3.2.1.7. Stability of the active substance (s)
3.2.2. Finished medicinal product
3.2.2.1. Description and composition of the finished medicinal product
3.2.2.2. Pharmaceutical development
3.2.2.3. Manufacturing process of the finished medicinal product
3.2.2.4. Control of excipients
3.2.2.5. Control of the finished medicinal product
3.2.2.6. Reference standards or materials
3.2.2.7. Container and closure of the finished medicinal product
3.2.2.8. Stability of the finished medicinal product
Particularities within the quality dossier für herbal medicinal products e.g.

“With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.”

“With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation."
Specific Guidelines for quality assessment of herbal medicinal products

Herbal Medicinal Products Committee (HMPC) at the European Medicines Agency (EMA)


e.g. quality of herbal medicinal products, specifications, quality issues related to combinations, stability testing, use of recovered solvents, essential oils, Q&A collection, new: draft „mock-up“ dossier (Appendix 2 to guideline on the use of CTD)
Guideline on Quality of Herbal Medicinal Products

(CPMP/QWP/2819/00) Information on active substance

"For standardised herbal preparations, the content of constituents with known therapeutic activity must be indicated with the lowest possible tolerance (with both upper and lower limits). In the case of active markers used for quantified extracts the content of the markers has to be given as a defined range. In the case of an analytical marker of an extract for which neither constituents of known therapeutic activity, nor active markers are known, the specified minimum and maximum content is related to the validated analytical range as a base for analytical suitability within the frame of batch related control." (Group III: "other" extracts according to Ph.Eur.)
Quality Issues Related to Combinations

"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."

"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."
CONTAMINANTS

- Plant protection products/pesticides
- Heavy metals
- Aflatoxins/mycotoxins
- Microbiological purity
- etc
PESTICIDE RESIDUES

- Ph. Eur. Chapter 2.8.13 (list containing 70 entries + limits)
- Substances not listed: Reference to food law (see below) or calculation of the limit
- Regulation No. 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin
- Database (by products and by substances): http://ec.europa.eu/food/plant/pesticides/pesticides_database/index_en.htm
PESTICIDE RESIDUES

Annexes to Regulation 396/2005

- I: (Groups of) products to which MRLs apply (including herbal teas)
- II: MRLs formerly defined for products under EC Directives
- III: Temporary MRLs for defined products
- IV: Substances for which no MRLs are required
- (V and VI not yet published, e.g. conversion factors for processed commodities)
- VII: Fumigants

Most important: Annex I, II and III
HEAVY METALS

- Ph. Eur. monograph "Herbal drugs"
  - Lead (Pb) 5.0 mg/kg
  - Cadmium (Cd) 1.0 mg/kg
  - Mercury (Hg) 0.1 mg/kg

Exemptions in individual Ph.Eur. Monographs e.g.

<table>
<thead>
<tr>
<th>Cd</th>
<th>Pb</th>
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<tbody>
<tr>
<td>Fumitory</td>
<td>Nettle root 7.0 mg/kg</td>
</tr>
<tr>
<td>Tormentil</td>
<td>Iceland moss 10.0 mg/kg</td>
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<tr>
<td>Willow bark</td>
<td>2.0 mg/kg</td>
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</tbody>
</table>
MYCOTOXINS

Ph.Eur. 2.8.18

- Determination of aflatoxin B1 in herbal drugs
- Limit: 2 µg/kg for B1; 4 µg/kg for B1, B2, G1, G2

Individual monographs

- Liquorice dry extract and Liquorice dry extract for flavouring purposes: 80 µg/kg ochratoxin A
- Liquorice root: 20 µg/kg ochratoxin A
MICROORGANISMS

Acceptance criteria Ph.Eur.

- Chapter 5.1.4. „Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use“
- Chapter 5.1.8. „Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation“
- Categories A, B, C dependent from pre-treatment leading to reduction of microbial load
MICROORGANISMS

Acceptance criteria Ph.Eur. 5.1.8, categories:

A. Herbal medicinal products containing herbal drugs, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (for example herbal teas, with or without added flavourings)

TAMC (2.6.12) Acceptance criterion: $10^7$ CFU/g
Maximum acceptable count: 50 000 000 CFU/g

TYMC (2.6.12) Acceptance criterion: $10^5$ CFU/g
Maximum acceptable count: 500 000 CFU/g

*Escherichia coli* (2.6.31) Acceptance criterion: $10^3$ CFU/g

*Salmonella* (2.6.31) Absence (25 g)
MICROORGANISMS

B. Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where the method of processing (for example, extraction) or, where appropriate, in the case of herbal drugs, of pre-treatment reduces the levels of organisms to below those stated for this category

TAMC (2.6.12) Acceptance criterion: $10^4$ CFU/g or CFU/mL
Maximum acceptable count: 50,000 CFU/g or CFU/mL

TYMC (2.6.12) Acceptance criterion: $10^2$ CFU/g or CFU/mL
Maximum acceptable count: 500 CFU/g or CFU/mL

Bile-tolerant gram-negative bacteria (2.6.31) Acceptance criterion: $10^2$ CFU/g or CFU/mL

*Escherichia coli* (2.6.31) Absence (1 g or 1 mL)

*Salmonella* (2.6.31) Absence (25 g or 25 mL)
MICROORGANISMS

C. Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where it can be demonstrated that the method of processing (for example, extraction with low strength ethanol or water that is not boiling or low temperature concentration) or, in the case of herbal drugs, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required under B

TAMC (2.6.12) Acceptance criterion: $10^5$ CFU/g or CFU/mL
Maximum acceptable count: 500 000 CFU/g or CFU/mL

TYMC (2.6.12) Acceptance criterion: $10^4$ CFU/g or CFU/mL
Maximum acceptable count: 50 000 CFU/g or CFU/mL

Bile-tolerant gram-negative bacteria (2.6.31) Acceptance criterion: $10^4$ CFU/g or CFU/mL

*Escherichia coli* (2.6.31) Absence (1 g or 1 mL)

*Salmonella* (2.6.31) Absence (25 g or 25 mL)
MICROORGANISMS

- Extracts: Category B or C, respectively
- Ph.Eur. Method of determination
  - 2.6.12 and 2.6.13: Microbiological examination of non-sterile products
  - 2.6.31: Microbiological examination of herbal medicinal products for oral use (and extracts): TAMC und TYMC according to 2.6.12 plus tests for specific microorganisms

HMPC Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products (published June 2015)
SUMMARY AND CONCLUSION

- Herbal medicinal products have to fulfil the same quality requirements like all other medicinal products.

- Due to their complex character (natural mixtures of ingredients) specific particularities do exist with regard to production (e.g. GACP) and quality control, e.g. tests on potential contaminants.