3.2.P. DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug product

3.2.P.2.1.1 Drug Substance

3.2.P.2.1.2 Excipients

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development
A brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the products used in supporting bibliographic data and the product described in P1 should be discussed, where appropriate.
Product development studies:

- Rational of the composition
- Compatibility of ingredients and container
- Optimisation of additives (Overages)
- Homogeneity
- Dissolution data
- Container
3.2.P. DRUG PRODUCT

3.2.P.2.2.2 Overages
3.2.P.2.2.3 Physicochemical and Biological Properties
3.2.P.2.3 Manufacturing Process Development
3.2.P.2.4 Container Closure System
3.2.P.2.5 Microbiological Attributes
3.2.P.2.6 Compatibility
The manufacturing process, within the meaning of this section, is the preparation of the herbal medicinal product from herbal substance(s) and/or herbal preparation(s). In the case of traditional herbal medicinal products for human use, the manufacturing process, within the meaning of this section, is the preparation of the herbal medicinal product from herbal substance(s) and/or herbal preparations and/or vitamins and/or minerals.

The description should include details of the process together with the controls exercised. This section should be in accordance with the ‘Note for guidance on manufacture of the finished dosage form’
3.2.P. DRUG PRODUCT

3.2.P.3 Manufacture
3.2.P.3.1 Manufacturer(s)
3.2.P.3.2 Batch Formula
3.2.P.3.3 Description of Manufacturing Process and Process Controls
3.2.P.3.4 Controls of Critical Steps and Intermediates
3.2.P.3.5 Process Validation and/or Evaluation
3.2.P.4 Control of Excipients
3.2.P.4.1 Specifications
3.2.P.4.2 Analytical Procedure
3.2.P.4.3 Validation of Analytical Procedures
3.2.P.4.4 Justification of Specifications
3.2.P.4.5 Excipients of Human or Animal Origin
3.2.P.4.6 Novel Excipients
Excipients

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON EXCIPIENTS IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT

London, 19 June 2007
Hilfsstoffe (EMEA/CHMP/QWP/396951/2006)

- Farbstoffe → LM Regularien
- Für Ph. Eur. Substanzen gelten die Anforderungen der allgemeinen Monographien
- Volle Anforderungen an Restlösemittel entsprechend CPMP/ICH/283/95
- Ph. Eur oder andere EU Pharmakopoe
- Nicht EU-Pharmakopoe → Validierung
- Alle anderen mit voller Spezifikation
- Neue Hilfsstoffe erfordern Daten, wie Wirkstoffe (Ausnahme: Sie werden in Lebensmitteln oder Kosmetika eingesetzt)
- Allgemein keine Forderungen zu Stabilitätsuntersuchungen
3.2.P. DRUG PRODUCT

3.2.P.5 Control of Drug Product
3.2.P.5.1 Specification(s)
3.2.P.5.2 Analytical Procedures
3.2.P.5.3 Validation of Analytical Procedures
3.2.P.5.4 Batch Analyses
3.2.P.5.5 Characterisation of Impurities
3.2.P.5.6 Justification of Specification(s)
Specifications for herbal medicinal products are linked to:

- quality of the herbal drug and/or herbal drug preparation
- manufacturing process (temperature effects, residual solvents)
- profile and stability of the active constituents/ formulation in packaging
- batches used in pre-clinical/clinical testing (safety and efficacy considerations)

Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially with regard to product-related substances, product-related impurities and process-related impurities.
Description: A qualitative description of the dosage form should be provided (e.g., size, shape, color). The acceptance criteria should include the final acceptable appearance at the end of the shelf-life. If color changes occur during storage, a quantitative procedure maybe appropriate.

b) Identification: Identification tests should establish the specific identity of the herbal drug(s) and/or herbal drug preparation(s), in the herbal medicinal product and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur traceability.

c) Assays:
   - markers
   - active constituents
   - impurities
   - excipients
The control tests on the finished product should allow the qualitative and quantitative determination of the composition of the active substance(s). A specification should be provided and this may include the use of markers where constituents with known therapeutic activity are unknown. In the case of herbal substances or herbal preparations with constituents of known therapeutic activity, these constituents should be specified and quantitatively determined. For traditional herbal medicinal products for human use containing vitamins and/or minerals, the vitamins and/or minerals should also be specified and quantitatively determined.
Verwendung von Leitsubstanzen zu Kontrollzwecken….

- Lagerung
- Prozess
- Identitätsprüfung
- Analytisches Verfahren
- chargenspezifische Kontrolle
- … individuelle Zwecke
### Allgemeine Klassifizierung der Inhaltsstoffe von Drogen bzw. daraus hergestellter Zubereitungen

<table>
<thead>
<tr>
<th>Klassifizierung der Inhaltsstoffe (Marker)</th>
<th>Klassifizierung der Extrakte nach Ph.Eur. 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.(^1) Wirksubstanzen/ wirksamkeits-</td>
<td>„standardisierte“ Extrakte(^2) (Typ A)</td>
</tr>
<tr>
<td>bestimmende Inhaltsstoffe</td>
<td></td>
</tr>
<tr>
<td>2.(^1) Wirksamkeits(mit)bestimmende</td>
<td>„quantifizierte“ Extrakte (Typ B1)</td>
</tr>
<tr>
<td>Inhaltsstoffe (pharmakol. aktive Substanzen)</td>
<td></td>
</tr>
<tr>
<td>3.(^1) analytische Leitsubstanzen</td>
<td>„anderere“ Extrakte(^2) (Typ B2)</td>
</tr>
</tbody>
</table>

\(^1\) bisher: normiert/eingestellt, \(^2\) bisher: standardisiert

*) Gemäß „EG-Guideline for herbal medicinal products“ werden die Inhaltsstoffe der Gruppe 1-3 unabhängig von ihrer therapeutischen Bedeutung dann als „Leitsubstanzen“ (= Marker) bezeichnet, wenn sie analytischen Kontrollzwecken dienen.
d) Impurities:

Impurities arising from the herbal drug(s) and/or herbal drug preparations e.g. contaminants such as pesticide/fumigant residues, heavy metals, are normally controlled during the testing of the herbal drug preparation (herbal drug).

e) Microbial limits

f) Shelf life

g) Biopharmaceutical properties of the dosage form (e.g. Dissolution / disintegration testing)
Testing for specific dosage forms (e.g. tablets)

a) Biopharmaceutical testing (e.g. Dissolution / disintegration testing)
b) Hardness/friability:
c) Uniformity of dosage units
d) Water content
Testing for specific dosage forms:

- Biopharmaceutical testing (e.g. Dissolution / Disintegration testing)
- Hardness/Friability:
- Uniformity of dosage units
- Water content
- pH
- Antimicrobial/Antioxidant preservatives
- Extractables from container/closure system
- Particle size distribution
- Redispersibility
- Rheological properties
Darreichungsformen im Arzneibuch (I)

Darreichungsformen, d. h. die Art, wie Arzneimittel verabreicht werden, sind Gegenstand allgemeiner Monographien zu jeder Darreichungsform und werden zusammen in einem bestimmten Kapitel präsentiert, das nach Art der Anwendung oder Gebrauch aufgebaut ist.

Dieses Kapitel umfasst alle Darreichungsformen von Kapseln über Zubereitungen zur Inhalation und Arzneimittelvormischungen bis hin zu Zubereitungen zur intramammären Anwendung für Tiere. Die Anforderungen in diesen Monographien, die für jede Darreichungsform essenziell sind und von der Art der Anwendung abhängen, sind für allein Europa vertriebene Arzneimittel ungeachtet des Wirkstofftyps verbindlich.
Dieser verpflichtende Charakter wird folgendermaßen begründet:

• Verweis auf die Anforderungen des Europäischen Arzneibuches unter F. Kontrolle des Fertigerzeugnisses in Teil 2 des Anhangs I der Richtlinie 2001/83 EG zu Humanarzneimitteln, in der geänderten Fassung der Richtlinie 2003/63/EG

Die Liste der Standardbegriffe für Darreichungsformen wurde als Sonderausgabe der Pharmeuropa und online veröffentlicht.
3.2.P. DRUG PRODUCT

3.2.P.6 Reference Standards or Materials
3.2.P.7 Container Closure System
3.2.P.8 Stability
   3.2.P.8.1 Stability Summary and Conclusion
   3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment
   3.2.P.8.3 Stability Data
2.2.1 General

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the active substance and the dosage form.

2.2.2 Photostability Testing

Photostability testing should be conducted on at least one primary batch of the finished product if appropriate. The standard conditions for photostability testing are described in the Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products (CPMP/ICH/279/95).

→ Normally not applicable for Herbal Medicinal Products
2.2.3 Selection of Batches

At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

Two options are acceptable:

a) For conventional dosage forms (e.g. immediate release solid dosage forms, solutions) and when the active substances are known to be stable, stability data on at least two pilot scale batches are acceptable.

b) For critical dosage forms or when the active substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be of at least pilot scale, the third batch may be smaller.
2.2.3 (continued)

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Where possible, batches of the finished product should be manufactured by using different batches of the active substance.

Stability studies should be performed on each individual strength and container size of the finished product unless bracketing or matrixing is applied.
Long term:

Every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

Accelerated:

A minimum of three points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended.

Intermediate:

A minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended. For herbal medicinal products on which the applicant in the possession of historical batch data, the testing frequency may be reduced if justified by the applicant.
## Stabilitätsprüfungen

<table>
<thead>
<tr>
<th>mode of storage</th>
<th>conditions</th>
<th>minimum time</th>
</tr>
</thead>
<tbody>
<tr>
<td>long term testing</td>
<td>25 °C +/-2 °C/60 % RH +/- 5 %</td>
<td>12 month</td>
</tr>
<tr>
<td>accelerated testing</td>
<td>30 °C +/-2 °C/75 % RH +/- 5 %</td>
<td>6 month</td>
</tr>
<tr>
<td>stress testing</td>
<td>40 °C +/- 3 °C/60 % RH +/- 5 %</td>
<td>6 month</td>
</tr>
</tbody>
</table>
### 2.2.7 Storage conditions (General case)

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage Condition</th>
<th>Minimum Data at Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT</td>
<td>25°C/60% RH OR 30°C/65% RH</td>
<td>6 months (a) or 12 months (b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No intermediate testing</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30°C/65% RH</td>
<td>6 out of 12 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C/75% RH</td>
<td>6 months</td>
</tr>
</tbody>
</table>
2.2.4 Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.
2.2.5 Specification

Stability studies should include testing of those attributes of the finished product that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.
Shelf life acceptance criteria should be derived from consideration of all available stability information. **It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage.** Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing. **A single primary stability batch of the finished product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes,** regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.
In the case of a herbal medicinal product containing a herbal substance or herbal preparation with constituents of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed ± 5% of the declared assay value, unless justified. In the case of a herbal medicinal product containing a herbal substance or herbal preparation where constituents with known therapeutic activity are unknown, a variation in marker content during the proposed shelf-life of ±10% of the initial assay value can be accepted if justified by the applicant.
Pharmaceutical Development

- "Specifications are legally binding quality standards that are proposed by the manufacturer and approved by regulatory authorities" → Shelf life specifications need to be established in advance and specific (stability problems of herbal medicinal products need to be considered already during pharmaceutical development).

- Validated assays and chromatographic fingerprinting need to be "stability indicating", ideally they should be in line with methods used for starting materials and herbal preparations.
## Specifications: shelf life versus release

<table>
<thead>
<tr>
<th>Additional tests</th>
<th>Skipped tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingerprinting</td>
<td>Identification</td>
</tr>
<tr>
<td>Degradation impurities</td>
<td>Uniformity of dosage units</td>
</tr>
<tr>
<td>Mycotoxines</td>
<td>Residual solvents</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Disintegrating</td>
<td>Pesticides</td>
</tr>
<tr>
<td>Water content</td>
<td>Fumigants</td>
</tr>
<tr>
<td>Preservative/Antioxidant effectiveness</td>
<td></td>
</tr>
<tr>
<td>Extractables form container/closure system</td>
<td></td>
</tr>
</tbody>
</table>

Data from stability testing may be used for justification of elimination of tests in release testing
Stabilitätsprüfung Phytopharmakla

Dosiergenauigkeit: Durch mögliche Ausfällungen kommt der Prüfung auf Dosierungsgenauigkeit bei flüssigen pflanzlichen Präparaten mit Tropfer besondere Bedeutung zu → Integraler Bestandteil der Laufzeitspezifikation.


Pharmazeutische Entwicklung: Im Falle von instabilen Produkten muss dargelegt werden, dass die Formulierung der Produkte dem Stand von Wissenschaft und Technik entspricht. Von Seiten der Industrie wurden dazu Einwände geltend gemacht, da man durch die Monographien häufig auf eine bestimmte Darreichungsform festgelegt ist.

Kombinationspräparate: In begründeten Ausnahmen ist es möglich auf die Bestimmung der Stabilität jedes einzelnen Bestandteils zu verzichten. Z. B. bei Kombination von Extrakten sogenannter Flavonoiddrogen, wenn neben den Flavonoiden keine anderen für die jeweiligen Kombinationspartner charakteristischen Leitsubstanzen zur Verfügung stehen.
## Definition der Lagerungshinweise

<table>
<thead>
<tr>
<th>Testing conditions where stability has been shown</th>
<th>Required label</th>
<th>Additional label, where relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>25°C/60 % r.F. (It) 40°C/75% r.F. (acc)</td>
<td>No labelling to be used</td>
<td>Do not refrigerate or freeze</td>
</tr>
<tr>
<td>25°C/60% r.F. (It) 30°C/60% r.F. (acc.)</td>
<td>Do not store above 30°C</td>
<td>Do not refrigerate or freeze</td>
</tr>
<tr>
<td>25°C/60% r.F. (It)</td>
<td>Do not store above 25°C</td>
<td>Do not refrigerate or freeze</td>
</tr>
<tr>
<td>5°C (It)</td>
<td>Store at 2°C-8°C</td>
<td>Do not freeze</td>
</tr>
<tr>
<td>Below zero</td>
<td>Store in a freezer</td>
<td></td>
</tr>
</tbody>
</table>