Stability testing for medicinal products prepared in accordance with homoeopathic manufacturing procedures

Recommendations on how to use the "Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products" (CPMP/QWP/122/02, rev 1) as at 23 June 2006

1. Introduction

In all authorisation/registration procedures, stability testing of medicinal products manufactured in accordance with homoeopathic manufacturing procedures is principally subject to the same requirements as those laid down in the "Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products" (CPMP/QWP/122/02, rev. 1). Because of the particularities of homoeopathic preparations, justified deviations from the Guideline or modifications within the scope of the Guideline can be accepted.

The purpose of stability testing is to find out whether and, if so, how far the quality of a finished product will change during storage under the influence of temperature, humidity and possibly light, and to specify shelf-life periods including storage conditions where necessary.

2. Object of testing

In the case of medicinal products manufactured in accordance with homoeopathic manufacturing procedures, stability testing should be performed on the relevant finished product.

The active substances should comply in all items (manufacture and testing) with the relevant monograph (of the German homoeopathic pharmacopoeia /HAB/ or a company monograph).

No stability tests on active substances are required if their starting materials are monographed in the HAB. In the case of company monographs evidence should be provided that the testing parameters used are relevant to stability (e.g. by specified zones in fingerprint chromatograms).

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1 in the following referred to as ‘Guideline’
2 In the case of liquid or solid dilutions intended for later use further processing must take place in the near future. If not, stability is to be specified on the basis of the “Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products” (CPMP/ICH/4104/00).
The tests should refer to the general and special stability relevant properties of the finished product and be based on the Ph.Eur. monographs for the relevant dosage forms, on the HAB manufacturing prescriptions as well as on the monographs of the starting materials and the preparations thereof with the lowest possible degree of dilution (HAB or company monographs). Whether substance-related stability testing and assaying should take place depends on the degree of dilution and the active substance content in the finished product. Omission of testing should be justified. Where the kind of active substance may be associated with health risks, assaying or determination of limits, where applicable, is required.

3. Test batches

According to the Guideline, option a), stability tests are required on two pilot batches or two production batches of the finished product. If various pack sizes are intended to be marketed, testing on each pack size is obligatory when different materials are used for primary packaging. Stability tests on a third batch are required in cases of critical dosage forms or known instabilities of the active substance.³

4. Testing frequencies

Since the stability profile of a finished product is derived from long-term tests the proposed shelf-life should be justified by data from tests on all stability-relevant parameters, conducted every three months in the first year, every six months in the second year and once a year thereafter. Deviation from this pattern should be justified. Testing frequencies for products stored under accelerated and intermediate conditions should be specified according to the Guideline.

5. Storage conditions

Finished product storage follows the terms laid down in the Guideline (see Table):

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage condition</th>
<th>Minimum time period covered by data at submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>25° C ± 2° C / 60 % RH ± 5 % RH or 30° C ± 2° C / 65 % RH ± 5 % RH</td>
<td>6 months (option a) 12 months (option b)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30° C ± 2° C / 65 % RH ± 5 % RH</td>
<td>6 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40° C ± 2° C / 75 % RH ± 5 % RH</td>
<td>6 months</td>
</tr>
</tbody>
</table>

³ See Guideline, 2.2.3 Selection of Batches, option b)
Compliance with the humidity requirements (see Table) is not obligatory if the primary packaging consists of impermeable material, e.g. ampoules.

Results from stability tests on products stored under intermediate conditions need not be presented.

Accelerated tests are principally required when active substance assaying in the finished product is obligatory.

According to Annex II of the Guideline, extrapolation of stability data is possible on the basis of accelerated test results.

According to the "Note for Guidance on Declaration of Storage Conditions"4, storage conditions derived from the stability tests should be included in the finished product labelling pursuant to sections 10 and 11 AMG.

6. Special requirements for stability testing

In accordance with point 2, the claimed shelf-life should be documented by relevant test results also for products manufactured according to homoeopathic methods.

However, in view of the particularities of homoeopathic products, deviations from these requirements are possible where justified. Homoeopathic products can be divided into three groups depending on the scale of testing required for products of different composition and the transferability of the results to other homoeopathic products.

6.1 Finished products containing mother tinctures or other preparations with the lowest possible degree of dilution (in the following shortened to ‘lowest dilution preparations’)

Finished products (monopreparations and combinations) containing mother tinctures or other lowest dilution preparations, are characterised by substance-specific properties of identity and possibly of content (see HAB monographs or company monographs).

Therefore, stability testing includes both the general stability properties of the dosage form and the substance-specific stability properties as well as the active substance content, where appropriate.

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4 Note for Guidance on Declaration of Storage Conditions:
A: In the Product Information of Medicinal Products
B: For Active Substances
(CPMP/QWP/609/96/Rev 1)
In products with mother tinctures or other lowest dilution preparations at concentrations between 1% and a calculated value below D6, substance-specific tests can be omitted if justified accordingly.

6.2 Finished products without mother tinctures or preparations with the lowest possible degree of dilution

If finished products (monopreparations and combinations) do not contain mother tinctures or other lowest dilution preparations but have different specifications, stability test results should be presented for each particular product.

Depending on the potency and the active substance content in these products, it may be necessary to conduct a substance-specific stability test and, where appropriate, an active substance assay, in addition to the testing of the general stability-relevant properties of the dosage form.

In justified cases, when the finished product contains toxicologically harmless active substances at calculated potencies greater than/equal to D 4, it is possible to present results from stability tests on reference products on the basis of the conditions specified under 6.3.2. It should be demonstrated by analytical test results that it is not possible to conduct substance-specific tests on the finished product itself.

6.3 Finished products containing active substances in higher potencies

6.3.1 In finished products (monopreparations and combinations) containing active substances only in higher potencies (calculated value greater than/equal to D 6), testing of the general stability-relevant properties of the finished product is sufficient provided interactions of any kind are reliably ruled out.

6.3.2 Under certain conditions the stability of a product as defined under 6.3.1 can be specified by reference to stability results for comparable products or, in justified cases, for products that are ‘free of active substance’. Comparability is assumed under the following conditions:

- reference products have same specification

- reference products are of same composition in respect of other ingredients (e.g. isotonicity agent), if contained

- same or at least comparable manufacturing procedure, same vehicle and kind of starting material (e.g. herbal)

- same specification of primary packaging material (complying with Ph.Eur.)

- manufacture of the products in the same company under comparable production conditions
- compliance with storage conditions and testing frequencies according to the Guideline (exception: Relative Humidity in the case of impermeable primary packaging material, e.g. ampoules)

- data from two pilot batches or two production batches each from at least five reference products.

Extrapolation of stability data according to Annex II of the Guideline is not possible.

7. **In-use stability**

As a rule, in-use stability data obtained according to the “Note for Guidance on In-Use-Stability Testing of Human Medicinal Products”\(^5\) should be presented in the case of finished products in multidose containers. Where appropriate, the requirements of 6.3.2 can be applied. Information on in-use shelf-life and in-use storage recommendations should be provided in the labelling of the finished product pursuant to sections 10 and 11 AMG, where necessary.

\(^5\) Note for Guidance on In-Use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99)