News:
Revision of WHO Stability Testing Guidelines

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These guidelines...

• ...have a long history (indicating their importance!)
• A very short update is presented here
The first WHO stability guidelines for pharmaceuticals

Initiated in 1988, published in 1996:
Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms

In focus:
- well established: mostly generics
- conventional dosage forms (e.g. tablets)
Its concept was based on climatic zones

- **Zone I** temperate
- **Zone II** subtropical, with possible high humidity
- **Zone III** hot/dry
- **Zone IV** hot/humid

Ref: Grimm, W., Drug Development and Industrial Pharmacy (1993) 19:2795-2830
Derived long-term storage conditions in 1996

<table>
<thead>
<tr>
<th>Climatic zone</th>
<th>℃</th>
<th>%RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>II</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>III</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>IV</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>
Developments in 2000

- Request from ICH to WHO to discuss the possibility of modifying the long-term conditions for zone IV to 30°C and 60% RH
- WHO Consultation procedure: discussion paper mailed to WHO experts with detailed rationale provided by ICH experts
Developments in 2001

- New alternative proposal to modify both ICH and WHO guidelines for zone IV to 30°C and 65% RH
- WHO consultation procedure:
  - discussion paper mailed to WHO experts
  - discussion during a WHO informal consultation
  - discussion during WHO Expert Committee on Specifications for Pharmaceutical Preparations
- Adoption of new condition for zone IV
Long-term storage conditions modified

- Zone I 21°C 45% RH
- Zone II 25°C 60% RH
- Zone III 30°C 35% RH
- Zone IV 30°C 65% RH*

*when special transportation and storage conditions were identified as being outside these criteria, additional study data supporting these conditions may need to be made available
ICH Developments  
2002 - 2003

- ICH Data package for registration in climatic zones II and IV (Q1F) signed off by all 6 ICH partners as step 2 document
- Consultative process in all three ICH regions by respective regulatory agencies
- Comments and new drafts circulated in ICH Expert Working Group
- Discussion at ICH meeting February 2003
- reached step 4
Developments in 2004, 1

Association of South East Asian Nations (ASEAN) holding several meetings on stability testing requirements

- in January 2004, based on real meteorological data, proposed new conditions for zone IV: 30°C and 75% RH
- opening again discussion at international level
- supported in various other countries, e.g. Brazil
Developments in 2004, 2

• In October 2004 the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended further international discussion.

• In December 2004 WHO organized a meeting involving major players, parties and regional harmonization groups:
  – options given for review by all WHO Member States and interested parties
  – discussion at international level to be continued
Developments in 2005

WHO Expert Committee on Specifications for Pharmaceutical Preparations
• discussed outcome of the 2004 WHO meeting and comments received thereafter
• recommended that WHO create:
  zone IVa: 30°C and 65 % RH hot and humid
  zone IVb: 30°C and 75 % RH hot and very humid
  then each WHO Member State should indicate which conditions would be applicable in its territory
Developments in 2006

Session and discussion among regulators from more than 80 countries at the 12th International Conference of Drug Regulatory Authorities (ICDRA) held in April in Seoul (Republic of Korea)
WHO Member States

1. should identify their stability testing conditions to facilitate import to and export from their country, ideally based on conditions currently being applied, thus avoiding the creation of barriers to access to medicines

2. should make information available to WHO regarding stability conditions to be applied within their markets

3. WHO should make available country information to facilitate its accessibility to manufacturers and any interested party on an international basis.
Further developments in 2006, 1

In June, ICH Q1F guideline withdrawn to leave definition of storage conditions in Climatic Zones III and IV (outside ICH regions) to the respective regions and WHO
Further developments in 2006, 2

In October the WHO Expert Committee on Specifications for Pharmaceutical Preparations

- endorsed the 12th ICDRA recommendations
- suggested revision of WHO guidelines on stability testing
- suggested the inclusion of a comprehensive list of WHO Member States' long-term stability testing requirements in the new guideline
Developments in 2007, 1

• Correspondence with major regional harmonization groups and WHO Regional Advisers requesting information on long-term stability conditions
• New WHO draft text prepared based on EMRO stability guideline
• First draft mailed for comments globally
• Collation of comments
• Discussion during a WHO consultation held in June
Development in 2007, 2

• Preparation of the **second draft**
• Second draft mailed for comments globally
• Collation of comments (mostly not for Zone IV!)
• Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations in October
• Not yet ready for adoption
Development in 2008

• Review an elaboration of comments by an expert
• In August, organisation of an informal workshop in Cairo (experts from all WHO Regions) to review comments and produce third draft for mailing worldwide
• Discussion during the 13th ICDRA in Berne
Next steps

• Collation of further comments
• Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations 13-17 October 2008
• Goal: adoption as new WHO guideline (by presenting WHO Governing Bodies for formal endorsement)
What's new in the proposed draft? 1

• **Scope covers:**
  – active pharmaceutical ingredients + pharmaceutical products
  – both marketed + new

• **Recommendation on labelling derived from stability studies (always specifying a temperature limit!)**

• **Additional advice given, e.g. model stability protocols/reports**
What's new in the proposed draft? 2

• Flexibility to accommodate (climatic conditions of the) intended market, i.e. current options for different long-term conditions: $25^\circ\text{C}/60\%\text{RH}$ or $30^\circ\text{C}/65\%\text{RH}$ or $30^\circ\text{C}/75\%\text{RH}$
• Different scenarios: "general case" (see above), "intended for storage in refrigerator" and "intended for storage in freezer"
• More definitions (e.g. ongoing stability study, tentative shelf-life, stability-indicating methods)
What's new in the proposed draft? 3

• Foresees also for products with "semi-permeable" and "impermeable containers" (includes approach for determining water loss)

• Inclusion of stress testing

• Inclusion of stability commitment, i.e. post-approval studies if data don't cover proposed re-test period/shelf-life (flexibility to allow for abridged submission for stable actives and products)
What's new in the proposed draft? 4

- Cross-reference to other guidelines, e.g. ICH texts on Photostability, Decision trees
- List of WHO Member States' required long-term stability conditions as per info received from countries (concept of classification of countries according to climatic zones abandoned) to make preference to provide "real" conditions required by national authorities - You are kindly requested to provide data!
Summary

• With this information,
• requesting your general support of the stability concept and the new draft guidelines
• I thank you very much for your kind attention!