

Stability Testing of Pharmaceutical Products in a Global Environment

Dr Sabine Kopp reports on the development of World Health Organization policy on stability testing.

Following lengthy discussions, the World Health Organization (WHO) has revised its guidelines on stability testing conditions for climatic zone IV, ie hot and humid countries. The guidelines are expected to be made available shortly. This article summarises the key events that have marked the WHO's work on developing international stability testing guidelines.

The stability of finished pharmaceutical products depends on several factors. On the one hand, it depends on environmental factors such as ambient temperature, humidity and light. On the other, it depends on product-related factors such as the chemical and physical properties of the active substance and pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system and the properties of the packaging materials.

For established drug substances in conventional dosage forms, literature data on the decomposition process and degradability of the active substance are generally available together with adequate analytical methods. Thus, the stability studies may be restricted to the dosage forms.

The actual stability of a dosage form will depend to a large extent on the formulation and packaging-closure system selected by the manufacturer. Stability considerations, for example selection of excipients, determination of their level and process development, should therefore be given high priority in the developmental stage of the product. The possible interaction of the drug product with the packaging material in which it will be delivered, transported and stored throughout its shelf-life must also be investigated.

The shelf-life should be established with due regard to the climatic zone(s) in which the product is to be marketed. For certain preparations, specific storage instructions must be complied with if the shelf-life is to be guaranteed.

The storage conditions recommended by manufacturers on the basis of stability studies should guarantee the maintenance of quality, safety and efficacy throughout the shelf-life of a product. The effect on products of the extremely adverse climatic conditions in certain countries to which they may be exported calls for special consideration.

To ensure both patient safety and the rational management of drug supplies, it is important that the expiry date and, where necessary, the storage conditions are indicated on the label.

The beginning

Work on stability of pharmaceutical products was initiated by the WHO in 1988 and the WHO *Guidelines on Stability Testing for Well Established Drug Substances in Conventional Dosage Forms* were adopted in 1996 by the WHO Expert Committee on Specifications for Pharmaceutical Preparations following extensive consultation¹.

In 2000, discussions began between the International Conference on Harmonization (ICH) expert working group Q1 (stability) and the WHO to harmonise the number of stability tests and conditions employed worldwide.

The working group, when developing guidance *Q1F Stability Data Package for Registration Applications in Climatic Zones II and IV*, proposed a modification to the WHO guidelines. The proposal concerned the long-term storage conditions for climatic zone IV (hot and humid countries). The group suggested that the WHO change its conditions from 30°C and 70% relative humidity (RH) to 30°C and 60% RH. A detailed paper including the rationale for the change was widely circulated for comment. Non-governmental organisations, international professionals' bodies and specialists, and members of the WHO expert advisory panel on the international pharmacopoeia and pharmaceutical preparations were among those consulted.

Responses to the proposal varied. A number of experts agreed that the proposal constituted a sound scientific approach. It was recognised that packaging was very important and common testing conditions should be agreed upon for WHO and ICH guidelines. Others criticised the approach as being too scientific and impractical while pointing out that actual meteorological and physical storage conditions in these countries would not allow simulation of long-term storage conditions as defined by the new proposal. Arguments were also put forward against the application of some parameters used in the calculations.

The stability of finished pharmaceutical products depends on environmental and product-related factors

ICH and WHO started discussions in 2000 to harmonise the number of stability tests and conditions employed worldwide...

...but there was little agreement from interested parties on an ICH proposal regarding long-term storage conditions in zone IV (hot and humid countries)

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In 2001, in a further round of discussions, it was proposed to change the real-time storage conditions for zone IV from 30°C and 70% RH to 30°C and 65% RH. This suggestion was again circulated widely for comments and the results discussed in July 2001.

In October 2001, the WHO expert committee modified the storage conditions and these were subsequently published in the WHO guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms, to read 30°C ($\pm 2^\circ\text{C}$) and 65% ($\pm 5\%$) RH for real-time stability studies defined for climatic zone IV. It was also agreed that where special transportation and storage conditions did not comply with these criteria, additional study data supporting these conditions might be needed^{2,3}.

ASEAN stability testing guidelines

The Association of South East Asian Nations (ASEAN) comprises Brunei Darussalam, Cambodia, Indonesia, Lao PDR (Laos), Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam. These countries are all situated in a hot and humid climatic zone (zone IV). ASEAN regulatory authorities have defined harmonised requirements for marketing authorisation for pharmaceuticals with a view to establishing a common market for their pharmaceutical products. This process includes harmonisation of requirements for stability testing.

Regulators and experts from ASEAN countries have met regularly with the WHO and experts from the International Federation of Pharmaceutical Manufacturers & Associations to discuss whether the conditions outlined in the WHO and ICH guidelines as described above are appropriate for countries which have vast areas with climatic conditions that are above the average RH and temperature used to characterise zone IV⁴.

After consultation and several meetings, a meeting held in Jakarta on 12-13 January 2004 concluded that the conditions described in the WHO and ICH guidelines cited above did not adequately address the climatic conditions prevalent in the majority of ASEAN countries. The conditions shown in Table 1 were then adopted for stability studies in ASEAN countries. Arguments supporting this conclusion have been set out⁵.

Table 1. Conditions for stability testing in ASEAN countries

Type	Conditions
Products in primary containers permeable to water vapour	30°C $\pm 2^\circ\text{C}$ /75% $\pm 5\%$ RH
Products in primary containers impermeable to water vapour	30°C $\pm 2^\circ\text{C}$ /RH not specified
Accelerated studies	40°C $\pm 2^\circ\text{C}$ /75% $\pm 5\%$ RH
Stress studies	Unnecessary if accelerated studies at above conditions are available

ASEAN based its considerations on the principle that testing should be biased towards more stressful rather than less stressful conditions so as to provide a margin of error in favour of the patients and to increase the likelihood of identifying substances or formulations that pose particular stability problems.

ASEAN also concluded that stability is obviously affected to a large extent by the permeability of primary packaging materials. Products packed in primary containers demonstrated to be impermeable to water vapour do not require testing at any specific RH, storage at constant temperature of 30°C throughout real-time testing being sufficient. However, guidelines will be needed to specify parameters, such as a thickness and permeability coefficient, which indicates demonstrated impermeability of packaging materials.

Implementation of the above decision will be preceded by a transition period during which existing national guidelines will still be applicable. In addition, a science-based approach will be taken to ensure correct evaluation when submitted data is based on conditions that are less stressful than those required (eg 30°C/65% RH). Factors to be taken into consideration include:

- complementary data provided to enable proper scientific evaluation;
- detected instability;
- data obtained under accelerated conditions;
- when more protective packaging is provided; and
- commitment to generate data under the new guideline conditions (30°C/75% RH, or 40°C/75% RH, or both) within a specified period.

A suitable label recommendation such as "Store below 30°C and protect from moisture" may also be applied.

ASEAN bloc countries rejected the conditions described in revised ICH and WHO guidelines...

...saying they were not appropriate for the climatic conditions in their countries...

different conditions for stability testing were adopted...

...and these will be implemented after a transition period

Next steps in WHO's harmonisation efforts

In view of the decisions taken by ASEAN as described above, the WHO responded with the following action plan. First, a WHO document was circulated in early 2004, in accordance with the WHO consultative procedure, to interested parties for consultation. The document requested comments on whether the WHO guidance on stability testing should be modified for long-term stability testing conditions (hot and humid climatic zone) and sought suggestions on how modifications should be implemented. Thereafter an informal consultation discussed comments received, in preparation for the meeting of the WHO expert committee on specifications which met in October 2004.

As the ASEAN guidance was confirmed and adopted, the WHO organised a meeting including ASEAN, WHO and ICH experts and other interested parties in December 2004⁶. The following recommendations were agreed during the meeting:

- the existing WHO guideline on stability testing should be reviewed in the light of new information on climatic conditions in zone IV as raised by the ASEAN countries; and
- all concerned parties represented at the meeting should return to their constituencies, consider the options that were discussed, and provide feedback and recommendations to the WHO, indicating preferences and giving reasons. Those parties will be invited to be involved in the continuation of the consultative process. The options are:
 - revert to 30°C/70% RH as the long-term stability testing condition for zone IV as it is likely that considerable data are already available. This might serve as a potential platform for future harmonisation between ICH and the WHO;
 - change to 30°C/75% RH as the long-term stability testing condition for zone IV in the interest of patient safety worldwide; or
 - add a new climatic zone IVb to accommodate hot and very humid areas (30°C/75% RH). The present zone IV (30°C/65% RH) would become zone IVa.

Feedback was requested by the end of March 2005. WHO member states not represented at the meeting were also invited to give their feedback.

Answers were received from the following member states and partners: Amazonian Countries (Bolivia, Brazil, Colombia, Cuba, Equator, Peru, Suriname and Venezuela), ASEAN (Brunei Darussalam, Indonesia, Malaysia and Thailand), ICH parties (the EU on behalf of European, Japanese and US regulators, as well as their respective industry associations), the South African Development Community (South Africa on behalf of SADC), the International Generic Pharmaceutical Alliance and the World Self-Medication Industry. There was no consensus among the various parties. Each option was favoured by at least one party.

Current status

Based on the above outcome, the experts who met during the 40th WHO expert committee meeting at the end of October 2005 had to take a decision about the WHO position for future stability testing. They were faced with a difficult situation. The WHO secretariat reminded the expert committee members that the WHO guideline had been revised in the light of harmonisation efforts in collaboration with ICH. After extensive discussion, the committee reached consensus that the WHO stability guidelines should be amended to reflect conditions for zone IV as follows:

- zone IVa – 30°C and 65% RH; and
- zone IVb – 30°C and 75% RH.

It was agreed that each individual member state within the former zone IV would need to indicate which of these conditions (zones IVa or IVb), would be applicable in its territory. This was intended to accommodate the two conditions currently in use.

The report and its outcomes, including annexes, ie the new guidelines adopted during the WHO expert committee meeting, are now with editors. It is expected that the recommendations and the report will be presented to the WHO executive board in May 2006 (final step). The report will be available thereafter on the web and in printed form⁷.

International Conference of Drug Regulatory Authorities

A discussion on stability conditions was held during the International Conference of Drug Regulatory Authorities (ICDRA) in Seoul in April 2006 (www.icdra.org). During this session, entitled "Stability: Global challenges for harmonisation", the following topics were addressed:

The ASEAN developments meant a decision would have to be made on whether to amend the WHO guidance

A decision was eventually taken to split zone IV into two zones, with zone IVb being hot and very humid areas and zone IVa being hot and humid areas

The official revised guideline could be available by the end of May 2006

- news from Asia: how to deal with real humid and hot storage conditions in ASEAN countries;
- what's new in the Americas? Stability testing for varying climatic conditions; and
- challenges for the ICH stability guidelines outside the ICH regions.

Recommendations from this meeting will be available on the WHO medicines website (www.who.int/medicines).

Future implementation

The WHO now wants member countries to tell it whether zone IVa or IVb would apply in their territory

It remains to be seen how these new conditions will be implemented in the WHO member states. The WHO would be very interested to receive information from its individual member states as to which of the above described conditions (zones IVa or IVb) would be applicable in their territory. The intention is to make this information easily accessible to third parties on an international basis and to see which of the two conditions is most commonly applied.

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