In December 2004 a meeting was organized to discuss “Stability studies in a global environment”. Details thereon, including the agenda, list of participants and recommendations, can be found on the web site: (http://www.who.int/medicines/organization/qsm/expert_committee/expertcomm.shtml)

The current document summarizes all comments received to date on the third options proposed at the above meeting. These comments will be presented to the forthcoming Expert Committee on Specifications for Pharmaceutical Preparations for discussion on the next steps to be taken.

We should like to take this opportunity to refer to WHO’s constitutional mandate to collaborate with all Member States, members of its Expert Advisory Panel, Collaborating Centres, nongovernmental organizations (NGOs) and other interested parties in a harmonized approach in the area of standards in quality assurance.

**RECOMMENDATIONS AGREED BY THE MEETING**

1. 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.

2. All concerned parties represented at the meeting should return to their constituencies, consider the options that were discussed, and provide feedback and recommendations to WHO, indicating preferences and giving reasons. Those parties will be invited to be involved in the continuation of the consultative process. The options are:
A. 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 harmonization between ICH and WHO.

B. Change to 30°C/75%RH as the long-term stability testing condition for Zone IV in the interest of patient safety worldwide.

C. 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 end March 2005 at the latest.

WHO Member States not represented at the meeting were also invited to give their feedback.

3. WHO should make the meeting materials publicly available via the WHO website, including the agenda, slide presentations, list of participants and their affiliations, the key points that were discussed, and the agreed recommendations.

FEEDBACK SUBSEQUENT TO THE MEETING ON STABILITY STUDIES IN GLOBAL ENVIRONMENT, 13-14 DECEMBER 2004

Indonesia would recommend option B to be applied in WHO Guidelines that is: change to 30 °C/ 75% RH as the long-term stability testing condition for zone IV in the interest of patient safety worldwide.

The reason for recommending this option is because it is the most suitable condition for ASEAN climate and the 9th ASEAN Consultative Committee for Standards and Quality (ACCSQ) Pharmaceutical Product Working Group (PPWG) Meeting, February 2005 held in the Philippines, decided to stick on this option.

I would be delighted to hear conclusion made by WHO as the result of recommendation gathering from all parties.
Dr L. Slamet, National Agency of Drug and food Control, Indonesia

With regards to the real time testing for ASEAN the chairman agreed that ASEAN keeps to the decision made at the 9th ACCSQ PPWG Meeting, 22-24 February 2005, Philippines.

On item 23(Agenda Item 5.3 ) the report of the 9th Meeting of the ACCSQ PPWG says that the meeting agreed to the proposal made by Indonesia and the Focus Discussion Group that "ASEAN to stay with the current real time and storage condition of 30 °C/ 75% RH". Hence this decision made would fall into option B: change to 30
Working document QAS/05.146 with comments

°C/75% RH as the long term stability testing condition for zone IV in the interest of patient safety worldwide.

With this the chairman would like the option B to be considered by WHO as ASEAN position which was the decision made at the 9th ACCSQ-PPWG and also support the position of Indonesia being the lead country for ACTD-Quality in particular on the Guidelines on Stability Studies for ASEAN region.

In addition Malaysia too agree with the decision made at the 9th PPWG Meeting i.e. the current real time and storage condition for ASEAN is 30 °C/ 75% RH which would falls into option B -establishing a global set of conditions for stability testing in hot & humid climates.

Dr F. Ariffin, National Pharmaceutical Control Bureau, Malaysia

WSMI member companies have considered the options provided by WHO (listed below) following the December 2004 meeting to discuss stability conditions to support hot and humid regions (Climate zone IV).

A 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 harmonization between ICH and WHO.

B Change to 30°C/75%RH as the long-term stability testing condition for Zone IV in the interest of patient safety worldwide.

C 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.

In terms of the 3 options presented, our preferences are as follows.

First (Option A).

To use 30/70 as the condition for all Zone IV countries. This option comes with the caveat that it becomes the single WHO condition for all countries in the agreed Zone IV. Where this is not the case and some countries within Zone IV still require testing at 30/75, Option C (second preference) becomes the preferred option.

If the 30/70 option is agreed, it is proposed that ICH should change the intermediate condition in Q1AR to 30deg and "at least 60% RH" (with a 5% engineering tolerance). Companies can then choose to run their studies under higher conditions (e.g. 70% RH if they so wish) and therefore have a single intermediate & Zone IV long term condition.
This option together with the proposed amendments to the ICH intermediate condition presents an opportunity for a global stability package thereby enabling timely access to new medicines in all territories of the world.

**Second (Option C).**

To use 30/75 as a Zone IVb condition for markets with very humid conditions, with Zone IVa continuing to accept 30/65 as their condition.

We continue to believe that the actual conditions in the majority of countries in Zone IV are adequately addressed by stability studies conducted at 30°C /65% RH as a long term stability test condition, and that only a minority of countries (very humid) may wish to consider long term stability testing at 30°C /75% RH.

This would mean that the standard global stability package, generated according to the ICH stability guidelines (30/65), would still meet the long term stability testing requirements of the majority of countries, apart from those in Zone IVB (very humid).

However, we recognize that the specific data stability data requirements for Zone IVB countries would still need to be met; but this could be achieved by supplementing the global stability data package with appropriate stability data at 30/75. If this option is agreed, then WHO should prepare an agreed list of the small number of countries that would be placed in the more humid zone IVb.

Only a minor revision to ICH Q1F, to reflect the new Zone IVB would be required and no change would be required to the current ICH Q1AR2 conditions, therefore this option has the advantage of not requiring yet another change to current global stability testing conditions and also a minimum change to the ICH guidelines.

This option allows stability data to be generated to specifically meet Zone IVB (very humid) conditions without imposing these more stressful humidity conditions to Zone IVa markets thereby minimizing the potential risk to shelf life and the need for more protective packaging and thus the impact on cost to a smaller number of markets.

**Third (Option B)**

To use 30/75 for all Zone IV countries. This option is strongly opposed as it could lead to the need to provide expensive and over-protective packaging for countries that do not need it, leading to higher costs and a higher packaging disposal requirement. Such conditions (75% RH) if imposed for all Zone IV markets would subject drug product to much harsher storage conditions than would be absolutely necessary according to measured conditions for a number of Zone IV markets and could lead to an adverse effect on product specifications, shorter shelf-life and increased costs resulting from over protective packaging.

In proposing a specific stability condition for one region only this negates the acceptance of a global stability package. This could impact on the availability of
medicines e.g. delays in submission or shortened shelf-life products and therefore have an impact on patient access to medicines.

If 30/75% is adopted for WHO Zone IV despite the opposition of Industry, then WSMI suggests that ICH conditions use the wording 30degC not less than 60% RH (similar to above)

Other Information

Whichever recommendation is made, it must be on the assumption that it becomes the single WHO condition for all countries in the agreed Zone IV. We would not expect to see the possibility that countries could adopt other testing conditions if they so wished. If the Zone is split into two, then WHO should prepare an agreed list of the small number of countries that would be placed in the more humid zone IVb.

New stability requirements introduced as a result of revised Zone IV conditions should take into account the totality of the stability data available for a product (including pharmaceutical development, drug substance stability and stability data under ICH conditions). Where the totality of this data is supportive consideration should be given as to whether a complete stability programme at the new Zone IV condition is required or whether it would be appropriate to supplement the package with appropriate stability data under Zone IV conditions.

In addition, WSMI members would expect to see an appropriate transition time (at least 3 years from guideline adoption), and an agreement that the new conditions, once adopted, would not be changed for a significant time - 5-10 years at least. In addition, WSMI is strongly opposed to the retrospective application of any new conditions unless it is clearly demonstrated on a case-by-case basis that a particular product is packaged inadequately.

WSMI would be pleased to be involved in any further consultations on this issue after WHO has received comments from all interested parties.
Dr D. E. Webber, World Self-Medication Industry, France and Dr P. Shah, GSK

Proposed Long-Term Stability Testing Conditions for Climatic Zone IV

ICH Position –

ICH partners, i.e. representatives of EFPIA, PhRMA, JPMA, FDA, MHLW and the EU, after having consulted their respective constituencies, classify the three options discussed at the WHO Stability Meeting in Geneva in December 2004, as follows:

- First preference:
  - Option 1, i.e. reversion to 30°C/70% RH as the long-term stability testing condition for Zone IV.
Second preference:
- Option 3, i.e. addition of a new climatic Zone IV b to accommodate hot and very humid areas (30°C/75% RH). The present Zone IV (30°C/65% RH) would become Zone IV a. This option requires a clear definition of countries falling under Zone IVb.

Least preference:
- Option 2, i.e. change to 30°C/75% RH as the long-term stability testing condition for Zone IV

In addition, ICH partners suggest that there is agreement between countries
- to define an implementation time of 3 years for the new conditions
- to commit not to change the agreed conditions for a period of 5 – 10 years
- not to apply the new conditions retrospectively to existing products.

Furthermore, ICH partners still feel that examples of active substances and drug products with stability problems in extreme conditions and of drug products that have been demonstrated as being stable for six months at 40°C/75% RH and 24 months at 30°C/65% RH, but have then shown to be unstable in the market, need to be provided and evaluated in order to provide a sound rationale and additional assurance for the definition of new storage conditions. The use of accelerated data, forced degradation studies on the active substance, data from pharmaceutical development and supportive data on the product should also be considered in this exercise.

Following a final decision on Zone IV long-term storage conditions, agreement needs to be reached on intermediate testing conditions for Zones I/II, possibly resulting in a revision of the parent ICH stability guideline.

Dr S. Keitel (ICH rapporteur), Germany

The ASEAN decision according to the 9th ASEAN Consultative Committee for Standards and Quality Pharmaceutical Product Working Group (ACCSQ/PPWG) meeting in February 2005 decided to choose 30°C/75%RH as a long-term stability condition.

Dr R. Govithavatanapong, Ministry of Public Health, Thailand

There was actually a presentation from Dr Manuel Zahn, AstraZeneca, Sweden, which addressed the various humidity conditions for stability.

It confirmed that for SADC the current stability conditions are acceptable. Although Dr Chukilizo of Tanzania indicated that they have an expert looking at the WHO proposals, it was agreed that, for the time being, the SADC stability guidelines remain unchanged.

Therefore, if we have to go for one of the three options for Zone IV, it will be option three, which includes the additional requirement for very high humidity conditions.

Dr E. Taute, SADC, South Africa
Result of the Workshop “Amazonian Countries Position Regarding Long Term Stability Conditions in WHO guidelines for Zone IV”
Dr R. D'Alessio, Regional Advisor in Medicines and Pharmaceutical Services
PAHO/WHO

As agreed in December 2004 during the meeting at WHO premises on Stability in Zone IV, attached please the Final Report (version in English as well as in Spanish). We have also included the list of participants.

The activity was organized by the National Drug Regulatory Authorities (ANVISA) and the PAHO/WHO office in Brazil.

Participants:
- Drug regulatory authorities from Bolivia, Brasil, Colombia, Cuba, Ecuador, Peru, Venezuela and Surinam.
- Susan Walters, WHO consultant
- Anvisa experts
- Brazilian academies experts
- Industry representatives
- Nelly Marin, PAHO representative

Summary points of discussion:
1. The shelf-live of a product depends of the maintenance of label strength until 10% of its value and no significant degradation of the product, which depends of the following external factors: light, humidity, temperature and packaging material,

2. There is a mathematical equation that relates environmental temperature and humidity and climatic chamber temperature and humidity,

3. Using this equation, reviewing some climatic data of a sample of cities, ICH decided to change the long term stability test in zone IV from 30°C/70% RH to 30°C /65% RH in 2003,
4. Drug regulatory authorities from Asian countries, using the same methodology, identifies the need to move to 30°C/75% RH for long term stability test to cover the real climate of important cities. Brazilian data using the same methodology shows that three provincial capitals (Manaus, Sao Luis and Macapa) are not covered by the parameters 30°C/70% RH, and six provincials' capitals are not covered by the parameters 30°C/65% RH (Manaus, Macapa, Sao Luiz, Teresina, Natal and Belem),

5. The mathematical equation used in this calculations are based in daily average temperatures which sub estimate the results if it is used daily maximum and minimum temperature instead,

6. Using 2003 data from US NOAA, in a sample of Latin American cities, two cities of Latin America: Panama and Barranquilla only will be covered using the parameters 30°C/75% RH,

7. There are populations living in very hot and humid areas in all countries near the equatorial line (Amazon area). To rely in label and packaging information that transfer the responsibility to pharmacy owners and consumers to store the medicines in particular temperature and humidity is unrealistic.

8. There are many different suppliers and specifications of semi-permeable packaging materials that can assure stability in 30°C and 75% RH when 30°C and 65% RH is not sufficient,

9. Study regarding humidity gain in tablets with different packaging material at 30°C and 65% RH, 70% RH and 75% RH shows that the difference in 5% of humidity in semi-permeable packaging materials can make a difference or not in humidity gain after 30 days depending of the packaging material.

Recommendations agreed by the meeting

1. The countries of Bolivia, Brazil, Colombia, Cuba, Equator, Peru, Suriname and Venezuela, on April 15th, 2005, in a meeting at PAHO office in Brasilia, decided unanimously to support the move towards 30°C and 75% RH in WHO guidelines for long term stability studies in Zone IV. The drug regulatory authorities presented in this meeting joint efforts to drug regulatory authorities from the Asian community to request WHO guidelines to move towards 30°C and 75% RH for long term stability studies in zone IV.

2. PAHO should participate in the following meetings regarding changes in WHO guidelines for long term stability studies in Zone IV.
3. The office of PAHO in Brazil will centralize the data gathering from the participants countries regarding one-year climatic data of major cities. The following parameters should be collected: dew point, maximum temperature, minimum temperature and atmospheric pressure. Professors of the University of Rio Grande do Sul – Brazil will analyze the data. Dr Susan Walters will advise them.

Brunei Darussalam was not aware that the decision on option B was not put through as official to the WHO. We have attended the focus discussion group on stability studies held in the Philippines last February prior to the 9th ACCSQPPWG Meeting and Brunei Darussalam is in full support of the decision that ASEAN had agreed on option B to be taken up as one of our stability requirement in stability studies to be conducted on pharmaceutical products registered and marketed in the ASEAN region.

Ms Z. Mahmud, Drug Quality Control Section, Ministry of Health, Brunei Darussalam

IGPA Comments on WHO Guideline on Stability Testing for Pharmaceutical Products

The International Generic Pharmaceutical Alliance (IGPA) welcomes the opportunity to comment on the options presented for possible changes to the World Health Organization (WHO) guideline on stability testing for pharmaceutical products. Three options for revision of the long-term storage condition for Zone IV countries resulted from the WHO meeting on Stability Studies in a Global Environmental held on December 13 and 14, 2004. These options may be summarized as:

1. Revert to WHO’s original 30C/70% RH
2. Modify to 30C/75% RH
3. Divide the world into Zone IVA and Zone IVB with a different storage condition for each.

Retaining the present Zone IV ICH and WHO condition of 30C/65% RH was not one of the recommended options. Yet, this is the approach that IGPA would recommend to WHO.

It is from the data presented at the December WHO meeting that the current 30C/65% RH condition is less stressful than the average climatic experience for some of the cities and countries that lie in Zone IV. However, the ICH guideline suggests special studies for those areas when necessary. Competent national authorities in those countries can require additional studies or conditions as they deem appropriate based on the specific meteorological condition in their country and specific products characteristics. Therefore, if scientific properties are applied properly and according to the current guidelines patient safety will not be compromised.

Each of the options suggested above will result in adding an additional stability storage condition for most global generic companies that conduct business both in the
ICH regions and Zone IV countries. This ultimately will have two undesirable outcomes in Zone IV countries: some generic companies will choose not to register their products in some of the countries reducing competition and thus raising prices, or even if they choose to register their products, the additional cost will be passed on to the customer.

Like WHO, most of IGPA member companies’ products and stakeholders are not presented not are covered directly by ICH guidelines, but the regulations and national guidelines for generic products are greatly influenced by the ICH Quality guidelines. IGPA therefore has similar interest to the international brand pharmaceutical industry in the establishment of worldwide harmonized regulatory guidelines in order to minimize duplicative or unnecessary testing. Harmonization should ultimately result in safer, more effective, and lower cost medicines available to more patients. In this regard the current ICH Q1F guideline, which harmonized a long-term storage condition for the world, although not perfect, was a major step forward for world health. If WHO moves forward with revising according to Option 1, 2, or 3, disharmony again will reign. Therefore IGPA recommends that WHO keep the current 30C/65% RH long-term storage condition.

Dr N. Cappuccino, Chair, IGPA Science Committee, Belgium

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