Recent Developments on Long-Term Stability Test Conditions

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Stability testing is the only way to demonstrate that the pharmaceutical product would meet the laid-down specifications within acceptance criteria throughout its lifetime. It is also required to gain the regulatory approval. The birth of International Conference on Harmonization (ICH) in 1991 and finalization of the guideline Q1A in 1993 led to harmonization of the stability test requirements for new drug applications, and was instrumental in development of a series of ICH and other National and regional stability guidelines, both for the new and existing drugs. There have been some recent developments, especially with respect to defining of storage condition for long-term stability testing. This note traces the new developments.

Background

If one looks back to the trend of recent developments related to International drug stability test guidelines, rationalization on a small aspect of drug stability test protocol, i.e, storage conditions for long-term testing, has stimulated most changes and even forced introduction, revision and/or withdrawal of some of the guidelines over the last few years. It all started in 2000, when a suggestion was put forward by the leader of the ICH Q1 Stability Expert Working Group to the World Health Organization (WHO), suggesting replacement of long-term testing condition of 30°C±2°C/70%±5%RH for Climatic Zones (CZ) III and IV in WHO guideline with 30°C±2°C/60%±5%RH, an intermediate testing condition for CZ I and II in ICH guideline Q1A. The document entitled *Harmonizing Stability Testing Requirements on a Global Basis*, containing the justification was forwarded by WHO to the experts and after receiving the comments, the agency announced changing of long-term testing condition from 30°C/70%RH to 30°C/60%RH. However, this was objected later by African countries, with the logic that 60%±5%RH was too dry for testing of products for distribution in some of the coastal African countries with very high humidity. A series of meetings hence followed in 2001 between WHO and ICH, and finally a decision was taken to change the WHO long-term testing condition from previously announced 30°C/60%RH to 30°C/65%RH, with an understanding that ICH intermediate testing condition would also be changed from 30°C/60%RH to 30°C/65%RH.

WHO made an announcement to the effect in 2002.[1] ICH followed by issuing a new guideline Q1F and revising the existing parent stability guideline Q1AR to Q1AR2 in 2003. The Q1F guideline defined an approach for broader use of Q1A recommendations for territories in CZ III and IV. In line with the Q1F recommendations, the intermediate storage condition for the `general case' in the Q1AR2 guideline was changed from 30°C/60%RH to 30°C/65%RH. Furthermore, this modified intermediate condition could be used as an alternative long-term condition to 25°C/60%RH for CZ I and II. It was mentioned that an alternative approach could be used if it satisfied the requirements of the applicable statutes and regulations.

Subsequent Developments

Discussions at the ASEAN forum

The Association of Southeast Asian Nations (ASEAN) comprises of members from Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos and Myanmar. ASEAN has a combined population of 890 million and now constitutes one of the fastest growing regions in the world. Efforts toward harmonization of ASEAN pharmaceutical regulations were initiated in 1992 through the ASEAN Consultative Committee for Standards and Quality (ACCSQ). The 13th meeting of the ACCSQ held in March 1999 in Manila agreed to set up a Pharmaceutical Product Working Group (PPWG), with Malaysia as the lead country. Accordingly, ACCSQ-PPWG was launched in September 1999 in Kuala Lumpur, Malaysia. The sixth meeting of the group was held on 4-6 September, 2002 at Siem Reap, Cambodia, which was preceded by the technical meeting of PPWG on product information and stability, where it was decided to harmonize stability test requirements among ASEAN countries. Agreement was reached on developing the

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first draft of working guidelines on Stability Studies, and the task was assigned to Indonesia. As all ASEAN countries fell in CZ IV (hot and humid climate), therefore, long-term stability test storage conditions were asked to be given a special focus, apart from harmonization of general stability testing requirements. The draft guideline and proposed long-term testing conditions were discussed in a meeting held at Jakarta from 12-14 January 2004. For the ASEAN, a long-term testing condition of 30°C±2°C/75%±5%RH was mooted, which was different from the one settled earlier by ICH and WHO (30°C/65%RH). Table 1 summarizes the test conditions prescribed by the ASEAN.

Table 1

Type of container/study	Storage condition
Products in primary containers permeable to water vapor	30°C/75%RH
Products in primary containers impermeable to water vapor	30°C/RH not specified
Accelerated studies	40°C/75%RH
Stress studies*	40°C/75%RH

*Stress studies were suggested to be conducted under accelerated storage conditions, but differently from registration batches. These were meant for analytical method validation, pharmaceutical formulation development, and identifying and monitoring potential degradation products during stability testing.

It may be pertinent to add here that the said ASEAN guideline was formalized on 22 February 2005 at 9th ACCSQ-PPWG meeting held at Philippines from 21-24 February 2005. The same is available under the title *ASEAN Guideline on Stability Study of Drug Product*.[2] The guideline addresses the information to be submitted in application for marketing authorization of drug products in ASEAN countries, and includes examples of a protocol of stability study, a report format, reduced design and extrapolation of data, and examples of types, thickness and permeability coefficient of packaging films. The drug products covered in this guideline include NCE, Generics and Variations (MaV and MiV), but exclude those containing vitamin and mineral preparations. As regards the long-term testing condition for ASEAN, it stuck to the decision of 30°C/75%RH. The same was even endorsed at the ICH-Global Cooperation Group meeting held recently at Yokohama, Japan.[3]

The parallel WHO activity

In light of the development on long-term testing condition at ASEAN, WHO invited feedback from experts on whether the current WHO conditions for long-term stability testing (real-time) should be changed from 30°C/65%RH to 30°C/75%RH, or back to 30°C/70%RH. The responses were discussed at the conference on *Stability Studies in a Global Environment* held at Geneva from 13-14 December 2004. The following options were recommended: i) 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; ii) Change to 30°C/75%RH as the long-term stability testing condition for Zone IV in the interest of patient safety worldwide; or iii) Add a new CZ IVb to accommodate hot and very humid areas (30°C/75%RH), turning the present CZ IV (30°C/65%RH) to become CZ IVa. Feedback on these proposals was requested by end of March 2005. These were later considered at the 40th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held at Geneva in October 2005. Therein, it was decided to split the current CZ IV into CZ IVa (30°C/65%RH) and CZ IVb (30°C/75%RH) to accommodate hot and very humid areas.

The proposed long-term testing conditions are given in Table 2.

Table 2

CZ	Climate	Criteria Mean annual temperature in opened air/Mean annual partial water vapor pressure	Long-term testing condition
I	Temperate	=15°C /=11hPa	25°C/60%RH
II	Subtropical and Mediterranean	>15-22°C />11-18hPa	25°C/60%RH
III	Hot and dry	>22°C/=15hPa	30°C/35%RH
IVa	Hot and humid	>22°C/>15-27hPa	30°C/65%RH
IVb	Hot and very humid	>22°C/>27hPa	30°C/75%RH

More details on the above-indicated developments are available at the WHO's website.[4]

Developments at ANVISA

Agçncia Nacional de Vigil?ncia Sanitaria (ANVISA, National Health Surveillance Agency of Brazil) passed a resolution in July 2005 in which it was mandated that testing at higher humidity is more adequate to Brazilian climate and conditions should be based on the maximum values measured. Accordingly, 30°C±2°C/ 75%±5%RH was recommended as the long-term testing condition, similar to the ASEAN developments. The sequence of changes in ANVISA requirements are summarized in Table 3.

Table 3

Guideline issue month/year	Resolution number, date	Long-term testing condition
April 2002	Resolução-Re No. 560, 2 April 2002	30°C±2°C/70%±5%RH
November 2004	Resolução-Re No. 398, 12 November 2004	30°C±2°C/65%±5%RH
August 2005	Resolução-Re No. 1, 29 July 2005, published 1 August 2005	30°C±2°C/75%±5%RH

Draft regional guideline for the Eastern Mediterranean Region (EMR)

The guideline *Stability Testing of Active Substances and Pharmaceutical Products* was developed during the WHO EMRO *Consultation on Regional Guidelines on Stability Studies of Medicines and Biologicals* held at Jeddah from 25-28 February 2006. Recently, the draft 2.0 of 19 April 2006 has been circulated by the WHO for comments and is recommended for adoption by the EMR regional committee. It is indicated the said guidance would eventually replace the original 1996 WHO's *Guideline for Stability Testing of Pharmaceutical Products Containing Well Established Drug Substances in Conventional Dosage Forms (*Annex 5 to the thirty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations). Similar to the concept taken by ENVISA, the EMR guideline suggests country-wise long-term testing conditions, based on the hottest and most humid CZ for a particular country. The country-wise information is reproduced in Table 4.

Table 4

Country	CZ II	CZ III	CZ IVa	Recommended long-term testing condition*
Afghanistan	+	+		30°C/65%RH
Bahrain				30°C/65%RH
Djibouti	+			30°C/65%RH
Egypt	+	+		30°C/65%RH**
Iran	+	+	+	30°C/65%RH**
Iraq	+			30°C/35%RH
Jordan	+	(+)		30°C/65%RH**
Kuwait	+			30°C/65%RH
Lebanon	+	(+)		25°C/60%RH
Morocco	+			25°C/60%RH
Oman	(+)	+		30°C/65%RH
Pakistan	+	+	+	30°C/65%RH
Palestine	+			25°C/60%RH
Qatar			+	30°C/65%RH
Saudi-Arabia		+	+	30°C/65%RH**
Somalia			+	30°C/65%RH
Sudan		+	+	30°C/65%RH**
Syria	+	(+)		25°C/60%RH
Tunisia	+	(+)		25°C/60%RH
UAE		+	+	30°C/65%RH
Yemen	+		+	30°C/65%RH

+CZ assigned; (+) Deserted part of the country; * The hottest and most humid CZ selected to establish the adequate stability-test conditions for a particular country; **Aqueous-based solutions in semi-permeable packaging, and dosage forms sensitive to low humidity, e.g. hard gelatin capsules, may require testing at low humidity according to the procedure described.

The guideline also provides recommended labeling statements for different testing conditions (see Table 5).

Table 5

CZs	Testing condition where the stability of the pharmaceutical product has been shown	Recommended labeling statement
I and II	25°C/60%RH (long-term) 40°C/75%RH (accelerated)	Store below 30°C*
III and IVa	30°C/65%RH (long-term) 40°C/75%RH (accelerated)	Store below 30°C
I and II	25°C/60%RH (long-term) 30°C/60%RH (intermediate)	Store below 30°C
III and IVa	30°C/65%RH (long-term)	Store and transport below 30°C
I and II	25°C/60%RH (long-term)	Store below 25°C

*No label storage condition required in this case in European Union.

The softcopy of the EMR guidelines is available on the web.[5]

Withdrawal of ICH Q1F

The outcome of the whole exercise at ASEAN and WHO level has a fall out in terms of withdrawal of the ICH guideline Q1F. The same was endorsed by the ICH Steering Committee at its meeting in Yokohama held on 6 June 2006. In a quick action, the guideline was withdrawn by ICH on 8 June 2006.

The explanatory note on the withdrawal of ICH Q1F at the ICH website[6] reads as follows 'ICH Q1F *Stability Data Package for Registration Applications in CZ III and IV* defined storage conditions for stability testing in countries located in CZ III (hot and dry) and IV (hot and humid), i.e. countries not located in the ICH regions and not covered by ICH Q1AR2 *Stability Testing for New*

Drug Substances and Drug Products. ICH Q1F described harmonized global stability testing requirements in order to facilitate access to medicines by reducing the number of different storage conditions. In the course of the discussions which led to the development of the guideline, WHO conducted a survey amongst their member states to find consensus on 30°C/65%RH as the long-term storage conditions for hot and humid regions. As no significant objections were raised in this survey, 30°C/65%RH was defined as the long-term storage condition for CZ III/IV countries in ICH Q1F. The document was adopted by the ICH Steering Committee in February 2003 and subsequently implemented in the ICH regions. However, based on new calculations and discussions, some countries in CZ IV have expressed their wish to include a larger safety margin for medicinal products to be marketed in their region than foreseen in ICH Q1F. As a consequence, several countries and regions have revised their own stability testing guidelines, defining up to 30°C/75%RH as the long-term storage conditions for hot and humid regions. Due to this divergence in global stability testing requirements, the ICH Steering Committee has decided to withdraw ICH Q1F and to leave definition of storage conditions in CZ III and IV to the respective regions and WHO. In assessing the impact of the withdrawal of ICH Q1F on intermediate testing conditions defined in ICH Q1AR2, the decision was reached to retain 30°C/65%RH. However, regulatory authorities in the ICH regions have agreed that the use of more stringent humidity conditions such as 30°C/75%RH will be acceptable should the applicant decide to use them.'

The European medicines agency announced the withdrawal vide document EMEA/ICH/421/02 in June 2006.[7] The withdrawal was adopted on 3 July 2006 by MHLW, Japan vide PFSB/ELD Notification n° 0703001. Similarly, CDER of USFDA released the withdrawal notice quickly on 6 July 2006.

The EMEA website[8] answers the following *Question* in the context of latest developments: Which kind of Stability Data is required for applications according to Article 58 of Regulation EC/726/2004? *Answer:* Article 58 of Regulation (EC) 726/2004 widens the scope of EMEA and CHMP to include applications for certain medicinal products intended exclusively for markets outside the community, e.g. for antiretroviral therapy. The agency may give a scientific opinion, in the context of cooperation with the WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the agency in accordance with the provisions of Article 65. The Committee for Medicinal Products for Human Use may, after consulting the WHO, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply. For these applications, it is of great importance to apply standards that ensure the same adequate product quality as for products to be marketed in the EU. In this context, stability data need to be submitted by the applicant that demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries, i.e. countries in CZ III and IV. Merely applying the same requirements as for the use in the EU, i.e. countries in CZ I/II, could potentially lead to substandard products when marketed in CZ III and IV. The guideline *Stability Data Package for Registration in CZ III and IV* (ICH Q1F) has been officially withdrawn by the ICH Steering Committee in June 2006 due to controversial discussions about the adequacy of storage conditions defined.[6] The WHO Expert Committee on Specifications for Pharmaceutical Preparations has decided to split CZ IV into CZ IVa (hot and humid) with storage conditions of 30°C/65%RH and Zone IVb (hot and extremely humid) with storage conditions of 30°C/75%RH; the WHO stability guideline will be revised accordingly. When evaluating applications under Article 58 of Regulation EC/726/2004, it has to be assumed that the respective medicinal product will be used in all sub-zones of

CZ III and IV, unless otherwise confirmed by the applicant. Therefore, in order to safeguard product quality throughout its entire intended shelf-life, stability studies under the conditions defined for CZ IVb need to be performed, i.e. the shelf-life needs to be established based on long-term data at 30°C/75%RH, supported by 6 months data at 40°C/75%RH. The principles of extrapolation described in the *Note for Guidance on Evaluation of Stability Data* (CPMP/ICH/420/ 02) as well as reduced testing designs as described in the *Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products* (CPMP/ICH/4104/00) may be applied. In cases where these data demonstrate stability over the required period of time, no special storage conditions need to be labelled. If an application under Article 58 of Regulation EC/726/2004 only contains data adequate for CZ I/II, the list of questions should request the respective data appropriate for CZ III and IV. If the data show stability problems at 30°C/75%RH with regard to humidity, the circulation/use of the product should preferably be restricted to those countries/regions that are covered by data, e.g. the product should only be used in countries within CZ III and IVa. As an alternative, storage conditions need to be labelled, including humidity, e.g. "Keep protected from ambient humidity" as especially for CZ IVb humidity may be the stability limiting factor. However, it has to be noted that due to the technical equipment and logistics available in some of the CZ IV countries as well as the education and compliance of patients in the respective area, exposure of the medicinal products to higher temperatures and humidity cannot be outruled. This needs to be taken into account when defining shelf-life and storage conditions. For products to be stored at "normal conditions", i.e. stable at 30°C, submission of accelerated data, i.e. 40°C/75%RH, can not be waived as they are needed to assess the impact of extreme temperature/humidity conditions that may occur in CZ IV, even though a product may not be stable for 6 months at these storage conditions. For aqueous products in semi-permeable containers to be marketed in CZ III, i.e. regions of extreme temperature, long-term testing should be performed at 30°C/35%RH. As an alternative, the calculation factors described in section 2.2.7.3 "Drug products packaged in semi-permeable containers" of the *Note for Guidance on Stability Testing of New Drug Substances and Products* (CPMP/ICH/2736/99) may be applied. Thus the above answer clarifies the most recent thinking of EMEA.

An opinion on global developments

The moot point is that the world is taking a U-turn with respect to drug stability test requirements. There was a positive move to harmonize the requirements under umbrellas of ICH and WHO, but now it is back to domination of regional guidelines. Atleast that is clearly visible - it was first ICH, then WHO, ASEAN, ANVISA and now WHO East Mediterranean Region and so on. The basic issue is whether the new WHO guideline, which will replace the 1996 document, will be brought out keeping the interests of >190 countries under WHO umbrella or it will meet only regional (like EMR) aspirations. It is appreciable that the activity has started towards revising the original text, but WHO should keep before it various International and regional guidelines, and propose a simple single model that is acceptable to most countries under its umbrella. It should develop a comprehensive table, as given in the Annexure of the draft EMR guideline (Table 4), and extend it to >190 countries suggesting their long-term testing conditions. That would help everybody.

Here the good points of pursuing for harmonization must be understood. Subsequent to the issue of main stability test guidelines by ICH, USFDA ventured to develop its own comprehensive guideline and uploaded the draft in 1998. The draft had several elements that were not yet discussed at the ICH forum, so it was natural for other ICH partners to raise serious reservations. The net result was that USFDA, the world's premier regulatory agency, could not finalize the guideline for almost 8 years. Finally, on 1 June 2006, the Department of Health and Human Services has announced the withdrawal of this guideline. The withdrawal notice was published in the Federal Register, Volume 71, No. 105, p. 31194.[9] USFDA has advised the industry to consult, as alternate resources, the ICH documents available on the FDA's website. That is the power of harmonization, which WHO has to pursue.

Coming back to splitting of long-term test condition into CZ IVa and IVb, and adoption of Zone IVb by several regions of the world on the name of patient safety, it would have been better if the original long-term test storage condition of 30°C/70%RH was retained by WHO, and ICH was also made to agree on the same as intermediate test condition for CZ I and II. This would have even been useful for Global harmonization.

There are several important aspects, related to the now agreed and adopted CZ IVb test condition, which are poorly understood. The first is that there is no sufficient experience on how the pharmaceutical products would tend to behave when stored at 30°C/75%RH for long periods of several years. Oppositely, there is rich experience in several parts of the world of testing at 30°C/70%RH, the original WHO's prescribed storage condition. The second is that most drugs show threshold relative humidity around 70%RH, beyond which moisture take-up increases in a

steep manner, especially by hygroscopic drugs. Figure 1 shows several examples of moisture uptake rate related to the relative humidity.[10]

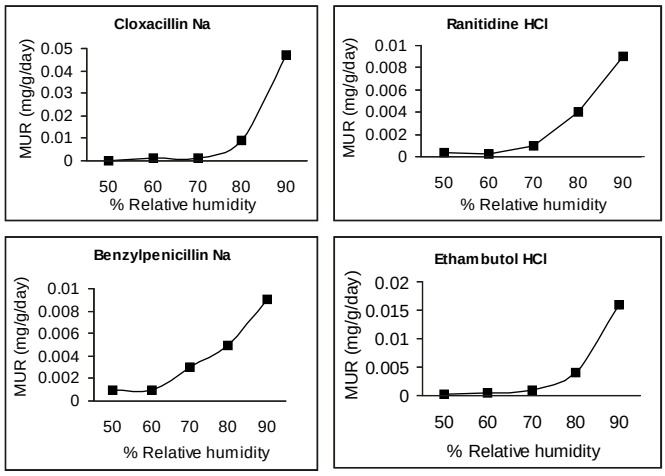

Figure 1. Moisture uptake rate (MUR) of hygroscopic drugs as a function of relative humidity

Clearly the sharp change is evident beyond 70%-75%RH. So the products, which may prove stable otherwise during testing at 30°C±2°C/70%±5%RH and even in the market place, may show instability during testing in more harsh humidity condition of 30°C±2°C/75%±5%RH, unnecessary forcing the industry to adopt barrier type of packaging, at added cost. Thirdly, it has been observed that sometimes the products fail after a year or two of storage at long-term conditions only with respect to LOD specifications. This is because packaging materials also have a life, and their permeability gets changed over the storage period. Once it happens during stability studies, the product can absorb higher extent of moisture and deteriorate faster during testing at 30°C±2°C/75%±5%RH than at 30°C±2°C/70%±5%RH. This means additional challenging requirement for formulation scientists to prepare products that can remain stable even on exposure to high humidity (75%RH) for long-term periods. Another argument in favor of suitability of 30°C/70%RH as long-term testing condition even for countries with very high humidity is the calculations of absolute humidity made during preparation of the ASEAN proposal. The ASEAN countries were found to have average environmental conditions of 27°C/79%RH, where the average absolute humidity worked out to be 0.0178. In comparison, absolute humidity at 30°C/70%RH calculated out to be 0.0188, which is higher than 0.0178. So the logic to adopt 30°C/75%RH as the long-term storage condition even for very humid countries is not strongly tenable. Hence, the fruitfulness of the whole global exercise to split CZ IV condition into CZ IVa and IVb is doubtful and can be put to question.

The stand of India in the process

The above-indicated developments have been watched with some interest in India. This is primarily because India exports pharmaceuticals extensively to most countries in the world, and any changes at International level impacts the testing in Indian industry in a big way. Several industry representatives and independent individuals from India responded to the feedback call by WHO on its initial three-tier proposal. A representative from India even attended the WHO conference on *Stability Studies in a Global Environment* held at Geneva from 13-14 December 2004.

However, our country subsequently failed to play any proactive role, and did not provide feedback on the proposals that emerged during the Geneva conference. India was not party to the final decision taken by WHO to split the storage conditions for CZ IV into CZ IVa and IV. The WHO working document QAS/05.146[11] provides comments received from different agencies and country representatives. It reports feedback from Indonesia; Malaysia; Thailand, Brunei Darussalam, South Africa, World Self-Medication Industry, France; ICH partners (EFPIA, PhRMA, JPMA, FDA, MHLW and the EU); Amazonian Countries (PAHO, ANVISA); and International Generic Pharmaceutical Alliance (IGPA). This reflects keen interest even of small countries in the Global decision process.

Thus it may not be out-of-context to advise that Industry Associations in our country should be more alert to proactively participate in International decision making, keeping into view India's status as the 4th largest producer of pharmaceuticals by volume. It has to be understood that one always stands to lose by being a follower of decisions taken by others.

In the withdrawal note of ICH Q1F, the definition of storage conditions in CZ III and IV have been left to the respective regions and WHO. In India, decision is yet to be taken with respect to categorization into recent classification of CZ (Tables 2 and 4). This needs to be done at the earliest.

Conclusion

It can be concluded, by taking note of the sequence of events in Table 6, that the long-term storage conditions for testing of pharmaceutical products have undergone repeated change over the last few years, and seemingly they are far from settled yet.

Rather the subject has become so touchy that decisions are being reversed under small regional influences. Unfortunately, the controversial decisions has lead to withdrawal of ICH guidance Q1F, leaving the whole of pharmaceutical industry outside ICH in confusion, to fend for itself. Here again the leading role of WHO is expected, and the revision being undertaken on their 1996 guideline, should encompass all countries falling under its umbrella. The revised guideline should be finalized after due consultation among the stakeholders, not to be influenced again by individual requests.

Table 6

Year	Guideline	CZ	Long-term storage condition	Intermediate storage condition
1993	ICH Q1A	I & II	25°C /60%RH	30°C /60%RH
1996	WHO guideline	III & IV	30°C /70%RH	----
2001	WHO Rev.1	III & IV	30°C /65%RH	
2003	ICH Q1AR2	I and II	25°C /60%RH	30°C /65%RH
2003	ICHQ1F	III & IV	30°C /65%RH	
2004/2005	ASEAN	IV	30°C /75%RH	
2005	WHO Rev. 2	III & IVa Ivb	30°C /65%RH	30°C /75%RH
2006	ICHQ1F is withdrawn			

On its part, Indian Industry in future should take a proactive role in the International specification setting process, and this can be done very confidently with the nature of expertise available in Industry and elsewhere.

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