

# Adoption and Reasons for Withdrawal of ICH Q1F Guidelines

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## ABSTRACT

ICH Q1 F guideline provided a stability data package for the registration applications of drug substance and drug product in Climatic Zones III (hot and dry) and IV (hot and humid). These guidelines were adopted by the ICH in February 2003 and subsequently implemented in the ICH regions. Due to some reasons the guidelines were withdrawn. This review article describes the development of the concept of the climatic zones, the introduction of the guideline Q1F, its adoption, objections to these guidelines, its withdrawal and reasons for the withdrawal and its alternative that was proposed.

**Key words:** Guidelines, ICH, Q1F, Stability, Withdrawal.

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## INTRODUCTION

Stability studies of a drug substance or a drug product are carried out to check how its properties change with time under the influence of various environmental factors like temperature, humidity and light. Shelf life of a drug product and the retest period of the drug substance can be estimated with the help of stability studies. The guidelines for the stability testing of drug substance and drug product are provided by ICH (International Conference on Harmonization), WHO and many other regional authorities. These guidelines provide the information that is to be submitted in registration applications for new chemical entity and associated drug products.<sup>3</sup>

### The development of the concepts of zones

In order to reduce the amount of long-term storage testing required, it was necessary to reduce the number of different long-term testing conditions to a sufficient extent. This approach was first time proposed by Paul Schumacher in year 1972 and Wolfgang Grimm in 1986 and again in 1998 when they defined four different long-term storage conditions keeping the climatic conditions into consideration of the target markets. The entire globe was divided into four different climatic zones and this concept was described in various regulatory guidelines and pharmacopoeias. This became an established standard in developing finished pharmaceutical products.<sup>9</sup>

ICH guideline Q1A (1993) that provides guideline for stability testing of new drug substances and products focused mostly on the ICH zones (I and II) at the time of its implementation.<sup>1</sup>

The first WHO stability guidelines were initiated in the year 1988 and published in 1996. These guidelines included the non-ICH regions as well (i.e. zone III and zone IV) along with the ICH regions. These guidelines were meant to focus on testing the stability of pharmaceutical products containing well-established drug substances in conventional dosage forms and generics. Its concept was mainly based on the climatic zones. The entire globe was divided into 4 different climatic zones.

- I. Zone I: Temperate: Kinetic average temperature 21°C and 45% of annual average relative humidity.
- II. Zone II: Mediterranean: Kinetic average temperature 25°C and 60% of annual average relative humidity.

III. Zone III: Hot and dry: Kinetic average temperature 30°C and 35% of annual average relative humidity.

IV. Zone IV: Hot and humid: Kinetic average temperature 30°C and 70% of annual average relative humidity.<sup>9</sup>

**Countries in various climatic Zones:** The distribution of the countries in various climatic zones are as per shown in Table 1.<sup>1</sup>

### Stability storage conditions as per ICH and WHO guidelines

#### ICH Q1A (Zones I and II)

Long term storage condition: 25 ± 2°C/ 60 ± 5% RH

Intermediate storage condition: 30 ± 2°C/ 60 ± 5% RH

Accelerated stability testing condition: 40 ± 2°C/ 75 ± 5% RH

#### WHO (Zones III and IV)

Long term: 30 ± 2°C/ 35 ± 5% RH (Zone III)

30 ± 2°C/ 70 ± 5% RH (Zone IV)

Accelerated: 40 ± 2°C/ 75 ± 5% RH

### The start of politics on long-term stability storage conditions

In July 2000 Dr. Nick Turner sent a paper to WHO on behalf of the ICH expert working group Q1(stability). The paper mainly focused on the rationale for the stability conditions for the climatic zone IV (hot and humid). He suggested that the storage condition of 30 ± 2°C/ 60 ± 5% RH would be sufficient for the climatic zone IV but WHO recommended the storage condition of 30 ± 2°C/ 70 ± 5%.<sup>1</sup>

WHO accepted the plea on majority recommendations by the experts and finalized the storage condition of 30 ± 2°C/ 60 ± 5% RH for long term stability studies for zone IV countries.

After this alteration in the storage condition, the guideline Q1A was termed as Q1A(R).

### Objection by African region

The limits of these newly proposed storage conditions were 30°C/ 55% RH to 30°C/ 65% RH as per Q1A(R), but the condition of 30°C/ 55% RH

is very dry for coastal regions of Africa, hence this storage condition had to be reconsidered by ICH and WHO.

After considering this, ICH and WHO came to a conclusion that, the intermediate storage condition for Zone I and II regions for general case and the long term storage condition for Zone IV region for general case were kept as  $30 \pm 2^\circ\text{C}/65 \pm 5\% \text{ RH}$ . This satisfied the need of the African countries since the limit of relative humidity was increased.<sup>1</sup>

**The following changes were made:** as a result, it was decided to introduce a new stability guideline for the countries belonging to climatic zone III and IV which will satisfy the needs proposed by these countries and name it as Q1F.

After the adoption of Q1F guidelines, following changes were made in the previous guideline Q1A(R) regarding storage conditions and the guideline was termed as Q1A(R2) in February 2003.

1. The intermediate storage condition was changed from  $30^\circ\text{C} \pm 2^\circ\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$  to  $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$  in the general case for drug substance and drug product.
2.  $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$  was considered a suitable alternative long-term storage condition to  $25^\circ\text{C} \pm 2^\circ\text{C}/60\% \text{ RH} \pm 5\%$  in the general case for drug substance and drug product.<sup>3</sup>

## Introduction of ICH Q1F guideline

Q1A(R2) provided the guideline for stability testing of pharmaceutical drug substances or product for application in other countries along with Europe, Japan and USA, which are present in climatic zone I and II. For the countries present in climatic zone III and IV this parent guideline could be useful, except the storage conditions.

The World Health Organization (WHO) published a guideline with the name 'Stability testing of pharmaceutical product containing well established drug substance in conventional dosage forms' and this guideline was updated in the 37<sup>th</sup> meeting of WHO expert committee which was held in Geneva (October 2001). This guideline provided the stability testing recommendations along with storage conditions for all four climatic zones.

In guideline Q1F the stability testing recommendations were mentioned keeping the WHO and ICH Q1A(R2) in mind. In order to harmonize with the long-term storage condition for zone III and IV regions ICH had to change the intermediate storage condition in general case to  $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ . This new established storage condition was also an alternative to  $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$  as a long-term storage condition in parent guideline for general case.

came into existence in 2003. The parent guideline was considered applicable to climatic zones III and IV except the long-term storage conditions, which were included in this Q1F guideline.

**Storage condition for general case as per Q1F:** Long-term storage condition:  $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$  (For 12 months)

Accelerated storage condition:  $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$  (For 6 months)

## ASEAN Objection to the revised stability guidelines

Association of South East Asian Nations (ASEAN) comprises of countries like Cambodia, Indonesia, Brunei Darussalam, Lao PDR (Laos), Malaysia, Philippines, Myanmar, Singapore, Thailand and Vietnam.<sup>1</sup> These countries are situated in climatic zone IV (hot and humid). Regulators and experts from ASEAN countries met with WHO and experts from International Federation of Pharmaceutical Manufacturers and Association on regular basis to discuss if the testing condition provided by the WHO and ICH guideline are appropriate for countries which are having such vast area and the climatic conditions present are above the average relative humidity and temperature used to characterize zone IV. After several discussions,

a meeting was held in Jakarta on 12-13 January 2004. In this meeting, it was concluded that the testing conditions described in WHO and ICH guideline did not adequately address the climatic conditions that is prevailing in majority of countries of ASEAN.

ASEAN proposed a change in the current guideline. They proposed that instead of  $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$  condition in long term storage, the condition should be changed to  $30^\circ\text{C} \pm 2^\circ\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$  or should keep the previous storage condition of  $30^\circ\text{C} \pm 2^\circ\text{C}/70\% \text{ RH} \pm 5\%$ .

## Reason for this change

ASEAN believed that the testing should be performed on more stressful condition rather than less stressful condition so that if any error occurs that will not harm the patient and will increase the chances of identifying the factor that could cause any particular stability problem.

**Attempts by WHO for harmonization:** ASEAN, ICH and WHO and other interested parties held a meeting in December 2004. The following recommendations were made in the meeting.

1. To revert the long-term storage condition for the regional climatic zone IV to  $30^\circ\text{C} \pm 2^\circ\text{C}/70\% \text{ RH} \pm 5\%$ .
2. To keep  $30^\circ\text{C} \pm 2^\circ\text{C}/75\% \text{ RH} \pm 5\%$  as long-term stability testing condition for zone IV.
3. To include a new climatic zone IV(b) that consists of hot and humid areas ( $30^\circ\text{C}/75\% \text{ RH}$ ) and the zone IV was termed as zone IV(a) ( $30^\circ\text{C}/65\% \text{ RH}$ ).<sup>10</sup>

March 2005 was the last date to receive the feedbacks. After all these attempts also no proper solution to this problem was found.

**Current Status:** A suggestion to split the current climatic zone IV (hot and humid) into two zones was made in the fortieth meeting of WHO Expert committee on specifications for pharmaceutical preparations held in Geneva in October 2005.

- Zone IV(a) (30 degrees Celsius and 65% relative humidity); and
- Zone IV(b) (30 degrees Celsius and 75% relative humidity)

It was agreed that each individual member state of zone IV would need to indicate whether the region comes in zone IV(a) or zone IV(b).<sup>10</sup>

## Rise in regional expectation

The guideline Q1F was adopted by ICH in February 2003. However, various regions in the climatic zone IV had their own expectation as far as the storage conditions were concerned. Therefore, they made necessary alteration in their own stability guidelines.

Long-term storage conditions recommended in some of the regional guidelines are as follows:

1. **ASEAN Guideline on stability study of the drug product:** The testing storage condition as per the ASEAN stability guidelines introduced in July 2004 are as per the Table 2:<sup>4</sup>
2. **Regional guideline for the WHO East Mediterranean Region:** The storage conditions to be followed as per the regional stability guideline of EMR is as in Table 3:<sup>5</sup>
3. **Mexican Standard NOM-073-SSA1-2005, Stability of Drugs and Medicine.** Table 4.<sup>7</sup>
4. **Productos Farmaceuticos. Estudios De Estabilidad Medicamentos Para USO Humano:** This is the regulatory guideline for the stability testing of the pharmaceuticals in Central America.

The storage conditions for general case as per this guidelines are as per Table 5:<sup>11</sup>

5. **Guideline for stability testing of new drug substance and products by SFDA (The Saudi Food and Drug Authority):**

**Table 1: Distribution of countries into four different climatic zones.**

Region	Zone I and II countries	Zone III and IV countries.
Europe	All countries	-----
America	Argentina, Bolivia, Chile, Canada, Mexico, Peru, Uruguay, USA	Barbados, Belize, Costa Rica, Dominican republic, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Brazil, Honduras, Columbia, Cuba, Nicaragua, Dutch Antilles, Panama, Paraguay, Puerto Rico, Venezuela,, Jamaica.
Asia	Afghanistan, Armenia, Azerbaijan, China, Georgia, Iran, Israel, Japan, Kazakhstan, Kirghizia, Korea, Lebanon, Nepal, Syria, Tadjikistan, Turkey, Turkmen, Uzbekistan.	Bahrain, Hong Kong, India, Indonesia, Iraq, Jordan, Qatar, Kuwait, Laos, Malaysia, Maldives Islands, Oman, Pakistan, Philippines, Saudi Arabia, Myanmar, Singapore, Sri Lanka, Taiwan, Kampuchea, Thailand, United Arab Emirates, Vietnam, Yemen, , Bangladesh.
Africa	Egypt, Libya, Morocco, Ruanda,Algeria, South Africa, Zambia, Namibia, Zimbabwe.	Angola, Ethiopia, Benin, Botswana, Burundi, Djibouti, Ivory coast, Gabon, Ghana, Guinea, Cameroon, Longo, Madagascar, Malawi, Mali, Mauritania, Liberia, Niger, Nigeria, Senegal, Sierra Leone, Somalia, Sudan, Gambia, Tanzania, Togo, Chad, Uganda, Central African Republic, Kenya, Zaire.
Australian	Australia, New Zealand.	Marshall Islands, New Caledonia, Papua-New Guinea, Samoa, Tonga, Fiji.

**Table 2: Storage condition as per ASEAN guidelines**

STUDY/TYPE OF CONTAINER	STORAGE CONDITION
Long term (for products in primary containers semi-permeable to water vapor)	30°C ± 2°C /75% RH ± 5% RH
Long term (for products in primary containers impermeable to water vapor)	30°C ± 2°C /RH not specified
Accelerated	40°C ± 2°C /75% RH ± 5% RH
Stress testing	40°C ± 2°C /75% RH ± 5% RH or at more stressful conditions.

**Table 3: Storage condition as per guideline for the WHO EMR**

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

**Table 4: Storage condition as per mexican regional guideline**

Type of study	Storage conditions	Minimal period
Accelerated stability	40°C ± 2°C / 75% ± 5% RH	6 months
Intermediate stability	30°C ± 2°C / 65% ± 5% RH	6 months
Long-term stability	25°C ± 2°C / 60% ± 5% RH or 30°C ± 2°C / 65% ± 5% RH	12 months

**Table 5: Storage conditions as per the regulatory guideline of central america**

Type of product	Storage condition
Solid dosage form	40°C ± 2°C / 75% ± 5%RH
For liquid and semisolid dosage forms	40°C ± 2°C

**Table 6: General storage condition as per SFDA guidelines**

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30°C ± 2°C/ 65% RH± 5% RH	12 months
Accelerated	40°C ± 2°C / 75% RH± 5% RH	6 months

**Table 7: Summary of the implementation of the stability guidelines**

Year	Guideline	Climatic zone	Long term storage condition	Intermediate storage condition
1993	ICH Q1A	I and II	25°C/60 % RH	30°C/60 % RH
1996	WHO guideline	III and IV	30°C/70 % RH	-----
2001	WHO Rev 1	III and IV	30°C/65 % RH	
2003	ICH Q1A(R2)	I and II	25°C/60 % RH 30°C/65 % RH	30°C/65 % RH
2003	ICHQ1F	III and IV	30°C/75 % RH	
2004/2005	ASEAN	IV	30°C/75 % RH	
2005	WHO Rev.2	III and IVaIVb	30°C/65 % RH	30°C/75 % RH
2006	ICH Q1F is withdrawn			
2009				

Guidelines for stability testing of active pharmaceutical ingredients and pharmaceutical products provided by WHO.

The final draft was proposed in May 2005. The following guideline defines the stability data package for a drug substance or drug product that is sufficient for registration within the GCC Countries.<sup>6,8</sup>

General storage condition as per SFDA guidelines are as per Table 6.

**6. Chinese Pharmacopoeia:** Chinese pharmacopoeia in its Appendix XX provide 'Guidelines for the stability testing for the drug substance and preparations'.

### With drawal of ICH Q1F guideline

Due to these differences in opinion regarding the storage condition for long-term stability testing of pharmaceutical drug substance and product among different regions of climatic Zone IV, ICH decided to withdraw the guideline Q1F and leave the definition of the storage condition in climatic zone III and IV to respective regions and WHO.

Q1F was withdrawn by ICH in year 2006.

### Explanatory Note on the Withdrawal of ICH Q1F for the ICH Website

ICH Q1 F Stability Data Package for Registration Applications in Climatic Zones III and IV defined storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IV (hot and humid), i.e. countries not located in the ICH regions and not covered by ICH Q1 A (R2) Stability Testing for New Drug Substances and Drug Products. ICH Q1 F 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 objection was raised in this survey, 30°C /65%, RH was defined as the long-term storage condition for Climatic Zone 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 Climatic Zone 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 Climatic Zones 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 Q1A (R2), 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.<sup>2</sup>

### Alternative provided by WHO

Due to withdrawal of ICH Q1F guideline WHO decided to prepare a new guideline to exemplify the core stability data package required for the registration of active pharmaceutical ingredients (APIs) and finished products (FPPs), replacing the previous WHO guideline published in 1996. The WHO expert committee on specifications for pharmaceuticals preparations agreed in October 2006 in general to prepare this working document as a draft that could serve as a replacement for the WHO 'Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms', and to include a list of long term stability conditions as required by WHO member states.<sup>1</sup>

Summary of the journey of stability guidelines is as per Table 7

## CONCLUSION

Considering the above-mentioned information, it can be concluded that in last few years there has been repetitive changes in long-term storage condition for testing of pharmaceutical product stability.

The subject had become so sensitive that the decisions were revised under various influences and the same lead to withdrawal of ICH guideline Q1F. In the year 2009 WHO again played a leading role by providing an alternative for ICH Q1F and until date, this guideline has been followed without influence of any individual request.

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## PICTORIAL ABSTRACT



## SUMMARY

- ICH Q1 F guideline provided a stability data package for the registration applications of drug substance and drug product in Climatic Zones III (hot and dry) and IV (hot and humid).
- These guidelines were adopted by the ICH in February 2003 and subsequently implemented in the ICH regions.
- Due to some reasons the guidelines were withdrawn.

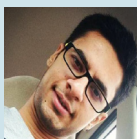
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