

# CONDUCTING STABILITY STUDIES - RECENT CHANGES TO CLIMATIC ZONE IV

AUTHOR: ULRICH MARKENS, REGIONAL HEAD ASIA-PACIFIC, SGS LIFE SCIENCE SERVICES

Stability testing is a routine procedure performed on drug substances and drug products to provide evidence on how the quality of a drug varies with time under the influence of a variety of parameters. Environmental factors such as temperature, humidity and light can potentially affect product quality and require establishing a re-test period for the drug substance or a shelf-life for the drug product and recommended storage conditions.

Any physical, chemical or microbiological change in the product potentially impact the efficiency and integrity of the final product and may therefore directly or indirectly impact patients' health. There are three major types of "changes":

- **Physical changes**, which might effect the appearance, melting point, clarity and color of solution, water, crystal modification (polymorphism) or particle size
- **Chemical changes**, which can be observed in an increase in degradation products or decrease of assay
- **Microbial changes**, like growth of microorganism, change in the efficiency of preservative contents (e.g., antioxidant, antimicrobial preservative)

Last but not least, some changes are due to the container closure system where functionality tests (e.g. dose delivery system) must be executed during the stability study in order to demonstrate full functionality of the entire "product" during the shelf-life period.

Stability studies are incorporated at all stages of the drug product life cycle - from early stages of product development to late stage follow-up stabilities. In particular the life cycle can be segregated into 6 different stages:

- Stage 1: Early stage stress- and accelerated testing with drug substances
- Stage 2: Stability on pre-formulation batches
- Stage 3: Stress testing on scale-up batches
- Stage 4: Accelerated and long term testing for registration purposes
- Stage 5: On-going Stability Testing
- Stage 6: Follow-up Stabilities

In early stages, stability studies are conducted on the API to gather information about physical and chemical properties (solubility profile, hygroscopicity, thermal - and chemical stability) and to determine a preliminary re-test period and storage conditions. Accelerated stability testing can be used as a "worst case" evaluation to uncover the kinds of degradation products

potentially found after long-term storage. Gentle conditions (recommended for long-term storage) and slightly elevated temperatures, can be used to determine the shelf-life of the product or the re-test period (expiration time) for a drug substance.

Depending on the stage of stability, product type and dosage form, the product is analyzed at intervals for various parameters. These parameters may include assays for the active ingredient, measurement of known degradation products, dissolution time, appearance, etc. Additionally, samples from production lots of approved products are retained for stability testing in case of product failures or production process changes. Retained samples can be tested alongside returned samples to determine whether the root cause of the problem was manufacturing or storage related.

## CLIMATIC ZONES

A very important point in conducting stability studies are the storage conditions. They should simulate the conditions under which the drug substance or drug product is subjected: from manufacturing to final application. Storage conditions are derived from real climatic conditions. Because most

chemical reactions follow logarithmic and not linear functions, this characteristic must be taken into consideration while defining appropriate conditions. Rather than calculating average temperatures, the mean kinetic temperature (MKT), expressed by the Arrhenius equation, is used.

The four major climate zones and the associated storage conditions stipulated in current stability guidelines are summarized in Table 1.

**TABLE 1. CLIMATIC ZONES AND ASSOCIATED STORAGE CONDITIONS**

Climatic Zone Countries	Calculated data			Derived data	
	Temp. °C	MKT °C	humidity % r.h.	Temp. °C	humidity % r.h.
<b>Climatic Zone I</b> "Temperate" Japan, United Kingdom, Northern Europe, Canada, Russia, United States	20	20	42	21	45
Storage condition acc. to ICH Q1A: 25°C / 60%					
<b>Climatic Zone II</b> "Mediterranean, Subtropical" Japan, United States, Southern Europe	21,6	22	52	25	60
Storage condition acc. to ICH Q1F: 30°C / 65% r.h					
<b>Climatic Zone III</b> "Hot, dry" Iran, Iraq, Sudan	26,4	27,9	35	30	35
<b>Climatic Zone IV</b> "Hot, humid" Brazil, Ghana, Indonesia, Nicaragua, Philippines	26,7	27,4	76	30	70

## REGULATIONS AND GUIDANCES

The ICH (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use) Guidelines Q1A(R2) "Stability testing of new drug substances and products" is the "gold standard" for conducting stability studies. This is valid for "new drug substances or drug products that

are sufficient for a registration application within the three regions of the EC, Japan, and the United States" - the intended scope of the guideline. Moreover this guideline (or previous version of it) forms the foundation for other guidelines published world-wide (Table 2).

To address the fast growing market segment, ICH Q5C "Quality of Biotechnological products – stability testing of Biotechnological/Biological products" must be emphasized as an important reference for stability of biopharmaceutical products.

**TABLE 2. GUIDELINES DERIVED FROM ICH Q1A(R2)**

Organization	Guidelines
<b>ASEAN</b>	Guideline "Stability Studies of Drug products"
<b>US-FDA</b>	Guidance for Industry "Stability Testing of Drug Substances and Drug Products; June 1998"
<b>WHO</b>	TRS 863, Annex 5: "Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms"
<b>EMA</b>	Note for Guidance on Stability Testing of existing active substance and Related Finished products (Draft), February 2002

Finally, discussions regarding stability testing for registration in Climatic Zone III and IV caused some confusion and uncertainties in recent years. At a WHO meeting, entitled "Stability Studies in a Global Environment," held in Geneva, December 2004, it adopted changes to stability testing requirements at an international level resulting in the following stability long-term study conditions for hot and humid climates:

- 30°C/65% e.g. WHO\*, ICH\*, SADC\*, GCC\*, Brazil
- 30°C/70% e.g. WHO previous, Cuba, Brazil previous
- 30°C/75% e.g. ASEAN\*

These changes were based on new calculations and discussions where some countries in Climatic Zone IV expressed their wish to include a larger safety margin for medicinal products to be marketed in their region than previously foreseen in ICH Q1F ("Stability Data Package for Registration Applications in Climatic Zones III and IV"). As a consequence, several countries and regions have revised their own stability

testing guidelines, defining up to 30°C/75 % 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 the definition of storage conditions in Climatic Zones III and IV to the respective regions and the WHO.

In assessing the impact of the withdrawal of ICH Q1F on intermediate testing conditions defined in ICH Q1A (R2), a decision was made to retain 30°C/65%. However, regulatory authorities in the ICH regions have agreed that the use of more stringent humidity conditions such as 30°C/75% will be acceptable should the applicant decide to use them.

At the 40th WHO Expert Committee Meeting (Oct. 2005), the Committee determined that the WHO stability guidelines should be amended to reflect conditions for Zone IV as follows:

- Zone IVa: 30°C / 65% r.h.
- Zone IVb: 30°C / 75% r.h

The Committee further resolved that each individual Member State within the former Zone IV will need to classify itself as Zone IVa or IVb. This process is still ongoing and leads into a situation where some of the benefits of the former "harmonized" system may be lost.

There are additional facts that need to be taken into consideration when registering products in Zone III/IV countries. Testing under more restrictive conditions might impact the packaging material used since it must be more protective. Also, early stage stability studies become more important, as manufacturers must clearly understand the robustness of their product in terms of sensitivity to moisture. Finally manufacturers must decide whether they are seeking a local / single country application versus a global approach. This decision will largely define the stability protocols. An example of a generic, global protocol is listed in Table 3 .

**TABLE 3. EXAMPLE OF A GENERIC, GLOBAL PROTOCOL**

Temp./ humidity	Condition	Climatic Zone	Timepoint									
			t=0	t=1	t=3	t=6	t=9	t=12	t=18	t=24	t=36	
25°C / 60% r.h	Long-term	I and II	X	-	X	X	X	X	X	X	X	X
30°C / 65% r.h.	Intermediate Long-term	I and II III and IV a	-	-	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
30°C / 75% r.h.	Long-term	IV b	-	-	X	X	X	X	X	X	X	X
40°C / 75 % r.h.	Accelerated	I, II, II and IV	-	(X)	X	X	-	-	-	-	-	-
50°C	Stress	-	-	(X)	X	-	-	-	-	-	-	-

## CONCLUSION

A successful stability study will establish the shelf-life date of the drug product, the retest period of a drug substance and appropriate storage conditions – but that's not all. A successful stability study must also ensure that patients receive a safe and effective medicine.

To ensure that this happens, drug manufacturers need to thoroughly follow regulations and guidelines and watch for material study results. Taking particular care in materials selection, tooling design and integrity testing is critical to the success of the product.

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*\* ASEAN: Association of South East Asian Nations - Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam  
GCC: Cooperation Council for the Arab States of the Gulf  
ICH: International Conference on Harmonization  
SADC: Southern African Development Community  
WHO: World Health Organization*

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## CONTACT INFORMATION

### EUROPE

#### BELGIUM

+32 10 42 11 11  
[be.lifeqc@sgs.com](mailto:be.lifeqc@sgs.com)

#### FRANCE

+33 1 41 06 95 93  
[fr.lifeqc@sgs.com](mailto:fr.lifeqc@sgs.com)

#### GERMANY (TAUNUSSTEIN)

+49 6128 744 245  
[de.lifeqc@sgs.com](mailto:de.lifeqc@sgs.com)

#### GERMANY (BERLIN)

+49 30 3460 7500  
[de.lifeqc@sgs.com](mailto:de.lifeqc@sgs.com)

### ASIA

#### INDIA

+91 44 2254 2601  
[in.lifeqc@sgs.com](mailto:in.lifeqc@sgs.com)

#### THAILAND

+662 294 7485 9  
[th.lifeqc@sgs.com](mailto:th.lifeqc@sgs.com)

### SINGAPORE

+65 677 53 034  
[sg.lifeqc@sgs.com](mailto:sg.lifeqc@sgs.com)

### CHINA

+86 21 6115 2197  
[cn.lifeqc@sgs.com](mailto:cn.lifeqc@sgs.com)

### HONG KONG

+852 260 99 611  
[hk.lifeqc@sgs.com](mailto:hk.lifeqc@sgs.com)

### TAIWAN

+886 2 2299 3279 ext 2500  
[tw.lifeqc@sgs.com](mailto:tw.lifeqc@sgs.com)

### NORTH AMERICA

#### CANADA

+ 1 905 890 4880  
[ca.lifeqc@sgs.com](mailto:ca.lifeqc@sgs.com)

#### USA (FAIRFIELD, NJ)

+ 1 888 747 8782  
[us.lifeqc@sgs.com](mailto:us.lifeqc@sgs.com)

#### USA (NORTHBROOK, IL)

+1 847 564 8181  
[us.lifeqc@sgs.com](mailto:us.lifeqc@sgs.com)

[WWW.SGS.COM/PHARMAQC](http://WWW.SGS.COM/PHARMAQC)