

## Stability tests in hot, wet climates – the global harmonization

### Introduction

**Stability testing for pharmaceutical products has now been harmonized globally. All pharmaceutical products must undergo defined specific testing conditions in accordance to local climatic conditions.**

With the ICH guideline Q1A (R2) for stability tests which was finalised in August 2003, and revised in 2005 (withdrawal of the chapter Q1F, which defines additional stress testing conditions in zones III and IV) new changes have taken place. With the withdrawal of chapter Q1F, the 10 member ASEAN countries have introduced their independent technical dossier related to the ICH guidelines and have adapted the testing conditions to suit their own climatic conditions. The enforcement of the ASEAN ICH guidelines into the ASEAN countries is currently in progress.

The example of the ASEAN countries clearly demonstrates that the testing standard will become more intensive and specific. Individual advances from various countries to look into testing protocols under varying climatic conditions or more toughened testing conditions are in discussion.

Once again the pharmaceutical industry sets new quality standards for the stability testing of pharmaceutical goods. It is a challenge for pharmaceutical companies but also a challenge to suppliers of testing equipment, to be prepared for the demands of tomorrow.

After the latest revision and implementation for ICH stability testing the actual conditions are as now regulated in chapter Q1A (R2) for climatic stability testing and in chapter Q1B for photo stability testing (unchanged). The introduction of the ASEAN ICH guidelines which are defined as zone IVb created new regional testing conditions for the long term stability tests to be carried out in the 10 ASEAN (Association of South East Asian Nations). This leaves now following climatic zones (Grimm, 1980). It is now up to individual countries located in zone IV to decide whether they wish to join the newly created climatic zone IVb or to follow the testing conditions of zone IV defined by WHO / ICH.

- Zone I: Temperate zone
- Zone II: Mediterranean/subtropical zone
- Zone III: Hot dry zone
- Zone IV: Hot humid/tropical zone
- Zone IVb ASEAN testing conditions hot/higher humidity

Chapter Q1A (R2) regulates the stability testing for long term testing at ambient, refrigerated and frozen storage conditions of pharmaceutical products. The testing conditions are displayed in table 1.

Table 1) Long term testing conditions

Climatic zone	Temperature	Humidity	Min. duration
Zone I	21 °C ± 2 °C	45% rH ± 5% rH	12 months
Zone II	25 °C ± 2 °C	60% rH ± 5% rH	12 months
Zone III	30 °C ± 2 °C	35% rH ± 5% rH	12 months
Zone IV	30 °C ± 2 °C	65% rH ± 5% rH	12 months
Zone IVb	30 °C ± 2 °C	75% rH ± 5% rH	12 months
Refrigerated	5 °C ± 3 °C	No humidity	12 months
Frozen	- 15 °C ± 5 °C	No humidity	12 months

Besides long term stability testing of various storage conditions, the ICH guidelines also requires accelerated testing conditions for all storage conditions (frozen, refrigerated and ambient) and an intermediate testing when the accelerated testing shows unacceptable deterioration (see table 2).

Table 2) Accelerated and Intermediate<sup>1)</sup> testing conditions

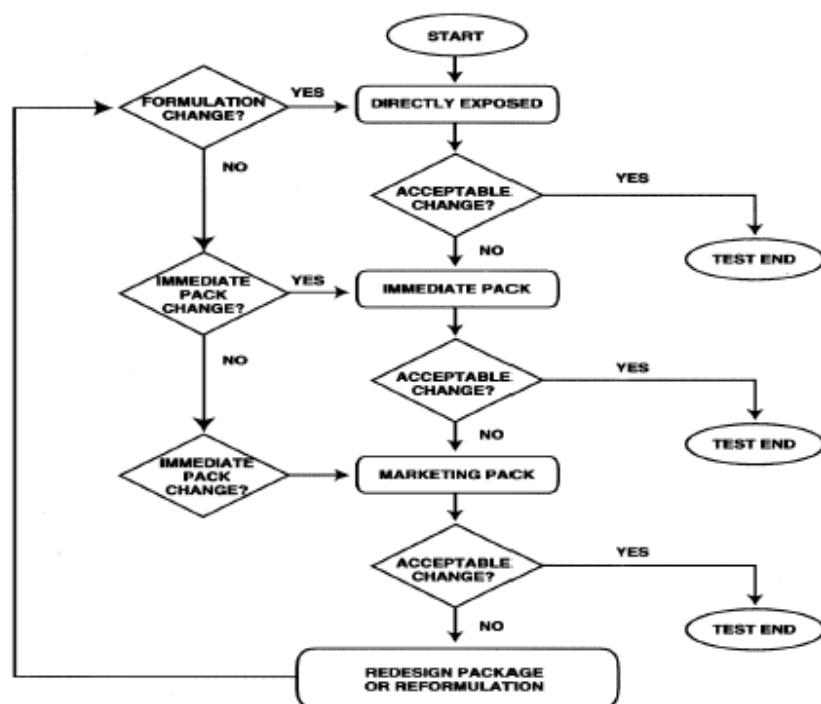
Climatic zone	Temperature	Humidity	Min. duration
Accelerated ambient	40 °C ± 2 °C	75% rH ± 5% rH	6 months
Accelerated refrigerated	25 °C ± 2 °C	60% rH ± 5% rH	6 months
Accelerated frozen	5 °C ± 3 °C	No humidity	6 months
Intermediate	30 °C ± 2 °C	65% rH ± 5% rH	6 months

<sup>1)</sup> zone II testing only when accelerated testing fails

While the exposure to climatic conditions in various climatic zones is undisputed and well accepted and carried out the photo stability testing in accordance to chapter Q1B is often not carried out or only sparsely performed. However the chapter describes the stability testing procedures for new substances and products which include generic pharmaceuticals as well. The graphic 1 shows the procedure of the photo stability testing

Graphic 1

**DECISION FLOW CHART FOR  
PHOTOSTABILITY TESTING  
OF DRUG PRODUCTS**



The chapter Q1B describes two options of light sources. Option 1 is a light mix of D65/ID65 daylight mix, xenon or metal halide light sources containing UV and daylight. However the UVB part needs to be removed and appropriate filters need to be installed. Option 2 is a two component light of UVA and visible light. These light sources are usually specifically designed for UVA (ICH compliant) and visible light. Filters are not necessary.

The use of option 1 and option 2 light sources depends on the application. In a R&D, where a big number of substances need to be tested in a short time, the use of xenon lights are advantageous (short exposure time), while to test final products the use of option 2 light sources are better suited to simulate actual storage conditions, without additional heat impact. Testing with option 2 is preferably to be carried out in climatic chambers as the unwanted effect of heating (caused by intensive light sources such as xenon) is eliminated and results give real data about light impacts and storage precautions for pharmaceuticals.

The exposure times are defined by the guidelines with a minimum of 1.2 Mio. Lux hours for visible light and 200Wh/m<sup>2</sup> for UVA light. It is important that the light intensities of samples are determined at the sample location. A recordable measurement at sample location will provide the necessary information about effective intensities and therefore required duration.

### **Higher demands on climatic chambers**

What is the purpose of stability tests in constant climate cabinets? And what role does the functionality of the chamber play in this? The idea is that stability tests should reliably indicate how and in what time the composition of a substance or packaged product changes under environmental conditions. This is done for the purpose of correctly determining and declaring the shelf life of substances, products and medications. In order to ensure that the process of making these determinations is carried out by uniform criteria worldwide, guidelines were developed, to be adhered to with regards to:

- temperature,
- humidity and
- light,
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and carried out in an identical manner. The existence of various climatic zones on the globe makes this uniformity a little complicated – as already explained. To meet today's demands, a climate cabinet should, where possible, be constructed to "replicate" all climatic zones. This is of particular importance for manufacturers of pharmaceutical products who export into various climatic zones. For these manufacturers, chambers such as the ones manufactured by BINDER are of interest, since they are able to "replicate" all climatic zones - and meet all international standards required for this purpose: they are in agreement with the pharmaceutical ICH guidelines and beyond this, the FDA, GLP/GMP etc.

### **More performance reserves needed**

The climatic chambers from the BINDER KBF series are already prepared for future demands today. Their test spectrum permits not only the 30 °C at 70 % r. H. required thus far, but also offers considerable performance reserves with options of 10 °C at 90 % r. H. They are open to all new standards, guidelines and changes. Therefore, those who are investing in a new climatic chamber today should look to the future. If testing must take place under other guidelines tomorrow, the chamber should be ready for it today.

### **Open to all demands**

Every user should check how open his products are to the demands of today and the near future. Manufacturers such as BINDER GmbH have thought about this well in advance and already have products on the market which meet all requirements. Chambers of the BINDER KBF series were constructed especially for the precise simulation of all climatic conditions with a constant climate, in accordance with the standards. This includes long-term storage and shelf life tests as per the pharmaceutical ICH guidelines and international standards. The KBF series guarantees high process security with tests which last for months under constant conditions, and precise, reproducible and constant humidity values in the entire work space. The humidity precision over time equals +/- 1.5 % r.H. Adherence to the ICH guidelines and international standards applies to all climatic zones – and this will remain true in the future as well.

### **System solutions are in demand – right through to SMS messaging**

Even today, BINDER offers a spectrum which reaches far beyond the normal range. It is important that BINDER offers not only a climatic chamber, but a complete solution – the climatic chamber, software, documentation, calibration / validation and service. Everything is possible - right through to automatic SMS messaging to the user in the event of an alarm. High operating comfort and flexibility are provided by a colour screen programme controller which shows the actual and set point values of all process figures at a glance and permits up to 25 programme processes to be saved. A built-in monitoring controller, numerous alarm functions and an integrated line recorder round up the offer.

### **New highlight for photo-stability tests (Q1B)**

Proof that the products do not or not significantly change within a certain period of use must, among other things, be provided through the photo-stability test with light. For this purpose, BINDER offers the complete solution on the market - the KBF with standard equipment of ICH-conforming lighting. *(image 2, legend: series KBF 720, with 700 l inner chamber volume)* The special international ICH guideline Q1B was created for proving photo-stability. Since the fulfilment of this guideline must now mandatorily be documented by the authorities without exception, pharmaceutical companies are faced by new challenges in this regard in their test practices. For the new photo-stability tests, samples must be exposed to a light amount of 1.2 million Lux\*hours, as well as UV radiation of 200 Watt\*hours /m<sup>2</sup>, in climatic chambers with ICH lighting. But what is the most objective method of proving these light values? The fundamental prerequisite for reliable recording is the integration and display of the light values on the regulator, as in the BINDER KBF series with ICH lighting. This includes the automatic shutoff of the lamps (VIS and UV separately) when the freely selectable dosage values are reached. Reliable recording of the light amounts is provided at BINDER with Light Quantum Control, two spherical light sensors *(image 3 legend: spherical light sensors)* which, due to their direction-independent characteristics, function more precisely than planar sensors. However, the following should be decisive for the testing authorities: BINDER chambers possess DataControlSystem software *(image 4, legend: Programme editor of APT-COM DataControl Software)*, and therefore, excellent options for documenting the test conditions in every phase. The information from the light sensors flows into this system, providing optimal proof.

### **Conclusion**

Permanent improvements of quality control protocols on a global platform requires flexible and easy to adjust climatic chambers. The withdrawal of Q1F and the introduction of ASEAN ICH guidelines is a clear indication that changes to improve the quality assurance for stability testing are present. Current discussion to consider temperature changes (cyclic testing of pharmaceuticals), the introduction of country (region) specific stress tests and the tightening of limits are possible adaptations in the future. It remains to follow – with some tension – how quick changes will be implemented. However, it is certain that higher demands are being placed on stability testing and high-performance systems which meet demands today and in the future are needed. Therefore users should consider the choice of product for their stability testing an investment in high performance is offering a far better degree of security and future adaptations today.