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Experts in Thermostatics

Stability tests according to ICH Q1A (R2)

Which tests are mandatory for the development and approval of new drug products and new drug substances and what are the most important requirements for a GMP-compliant climate chamber?

Contents

Summary

In 1990, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was born. This paper summarises the main contents of Guideline ICH Q1A (R2), which deals with the stability testing of new drug products and new drug substances.

The first part describes the general objectives of stability tests, the second part deals specifically with stability tests according to ICH Q1A (R2). Most of the stability samples are stored under standard climates. The third part of the paper therefore describes the most important requirements for a GMP-compliant climate chamber. In the last part, stability and climate tests from other industries are presented.

1. What are stability tests?

The requirements for quality, harmlessness to health, efficacy and safety of pharmaceuticals, cosmetics, foodstuffs and their active substances and ingredients have grown steadily over the past decades. International guidelines and standards such as the ICH Guidelines, WHO Technical Report 953, Annex 2, ASEAN and GMP ensure the international comparability of the required quality tests such as stability tests.

With the help of stability tests, manufacturers of pharmaceuticals, cosmetics and foodstuffs find out under which conditions the microbiological, chemical and physical stability of products and individual substances changes under constant ambient conditions. They are stored for a certain period of time in a controlled test environment. Depending on the test concept, this is defined by parameters such as temperature, humidity, light, oxygen and pH value. Any deviations from the target product profile are then established using appropriate analytical methods. As the case may be, a variety of properties such as active ingredient content, protein and vitamin content, toxicity of degradation products, colour, taste, nutritional value, solubility, moisture content or texture are included in the study. The results also provide information on the shelf life and expiry date as well as storage and transport conditions. For the storage of the stability samples, quality and testing laboratories use climate chambers, for larger volumes also walk-in climate chambers.

2. ICH Guideline Q1A

2.1. Aims of the ICH

The ICH was founded in 1990 as the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use with the aim of harmonising the assessment criteria for human pharmaceutical products as the basis for market approval in Europe, the USA and Japan. The founding members were the competent authorities in Europe, the USA and Japan as well as the respective associations of pharmaceutical manufacturers. Nowadays, numerous other institutions and authorities are members or have observer status, such as the WHO. In many cases ICH's guidelines are used internationally as a reference.

Up to that point, the authorisation of a new pharmaceutical product was a huge financial and time cost as each market in which it was to be introduced had its own rules and conditions. The main objectives of the initiative were to avoid repetitive testing, to harmonise the documentation to be submitted and to drastically reduce the number of clinical studies and animal experiments – while naturally always maintaining the highest standards of quality, safety and efficacy.

2.2. Underlying climate zone

Within the ICH quality guidelines, guidelines Q1A (R2) to Q1E are dedicated to stability testing of new drug products and new drug substances. The original guideline Q1F recommending stability testing for pharmaceutical products or active substances manufactured in climate zones III or IV (hot-dry and hot-humid) was withdrawn in 2006. Specifying the test conditions is left to the WHO and the regulatory authorities of the respective countries.

The most important factors influencing stability are temperature and humidity. In general, the pharmacology of the choice of test climates is based on the specifications for five main climate zones, which take into account the differences in temperature and humidity stress to which a drug is exposed during transport, storage, etc. The climatic conditions in Europe, the USA and Japan fall predominantly into climate zones I and II, therefore the ICH guidelines are based on this combined climate zone.

Stability zones

Zone	Type of Climate
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

ICH/WHO stability zones

2.3. Types of stability tests according to ICH Q1A (R2)

Stability tests according to ICH Q1A (R2) are intended to provide information on the stability of the chemical-physical properties of new drug substances and new drug products under its anticipated conditions of transport, storage and use. Stability data are logged and submitted to the Medicines Agency as part of the marketing authorisation application, together with information on shelf life, use-by dates and storage conditions.

Stability tests are not only relevant during the pre-registration phase. The stability of pharmaceutical products and active ingredients is also constantly monitored in the development phase, during pre-formulation and formulation as well as during ongoing production. The basis is the specification in which the test parameters and limits, e.g. for appearance, active substance content, decay times, colour, mass, microbiological purity and contamination of the pharmaceutical substance by decomposition or transformation products, are defined. The appropriate analytical method to demonstrate compliance with the specification (to the end of the shelf life and under the specified storage conditions) must be validated for each study according to the latest scientific knowledge and standards.

	Storage time (months)						
Storage condition	**1 month**	**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**
40°C/75% RH	X	X	X				
30°C/65% RH	X	X	X	X	X	X	
25°C/60% RH	X	X	X	X	X	X	X

Example of stability protocol

2.3.1. Stress test

In stress tests, the external stresses acting on the active ingredient or the pharmaceutical product are intensified in order to accelerate the chemical and physical degradation and thus shorten the test period. They are usually performed before the actual formulation. Stress tests support the determination of the analytical methodology and the selection of manufacturing technologies, provide information about the intrinsic (from the inside out) stability of the active substance as well as about decomposition processes and reactions with excipients. In addition, they provide information on the effects on stability of short-term deviations from storage conditions, e.g. during transport or overheating of the storage space. The most important test parameters are pH value, light, temperature, active substance concentration and oxygen. There are no general rules for carrying out stress tests. However, the ICH suggests that temperatures of 10°C above those of an accelerated test and at least 75 relative humidity should prevail in the test environment. The ICH regulations for testing photostability (lightfastness) are summarised in the Guideline ICH Q1B.

2.3.2. Long-term, accelerated and intermediate tests

The regulations on pharmaceutical product quality require the manufacturer to specify an expiry date – in the case of drug substances - a retest date. In accordance with the ICH Guideline, Accelerated Testing (accelerated study) and Long-Term Testing (long-term study) of three production batches each will be conducted for registration with the Medicines Agency. Interactions between the active ingredients and excipients with the packaging material, which influence the stability, must also be excluded. Therefore, in addition to the formulation, the test packaging must also be identical to the primary packaging in which the product is marketed after approval.

Long-term tests are carried out according to the intended storage conditions in the climate chamber, refrigerator or freezer. The test period must provide binding predictions of stability for the whole duration.

After approval, the EU GMP guide (**G**ood **M**anufaturing **P**ractice) in Chapter 6 (following FDA and ICH regulations for active substances) **prescribes ongoing stability programmes** (Ongoing Stability Studies). This should include at least one batch per year of each manufactured product for each strength and, if necessary, for each primary packaging material. If manufacturing processes or packaging change, additional samples should be taken. Ongoing stability tests are mainly designed to monitor whether the product meets the specified stability criteria throughout its shelf life. As long as no other test conditions are justified, they are carried out under the long-term conditions according to ICH.

Accelerated tests take advantage of the fact that the vast majority of chemical reactions are accelerated under the influence of temperature and humidity. By increasing the test parameters temperature and humidity, statements about the stability can be made more quickly.

If during accelerated testing of a product intended for storage in climate zones I and II "significant changes" occur – i.e. the limits described in the specification are exceeded – investigations should be conducted immediately on the samples stored under intermediate conditions (Intermediate Test).

2.4. Test conditions according to ICH Q1A (R2)

The ICH Guideline Q1A (R2) describes the general test conditions, the minimum storage period for the registration batches and the sampling intervals.

Stability Study	Storage conditions	Minimum time period	Testing Frequency
Climate Zone I + II Storage			
Long-term (choice of storage conditions)	25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months	each 3rd month 1st year, each 6th month 2nd year, annually thereafter
Intermediate (if long-term condition is 25 ± 2°C/60% RH ± 5% RH)	30°C ± 2°C/65% RH ± 5% RH	6 months	minimum three time points (e.g. 0/3/6)
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months	minimum four time points (e.g. 0/6/9/12)
Long-term (only semi-permeable containers)	25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 months	each 3rd month 1st year, each 6th month 2nd year, annually thereafter
Accelerated (only semi-permeable containers)	40°C ± 2°C/not more than ± 25% RH	6 months	minimum four time points (e.g. 0/6/9/12)
Refrigerator Storage			
Long-term	5°C ± 3°C	12 months	each 3rd month 1st year, each 6th month 2nd year, annually thereafter
Accelerated	30°C ± 2°C/65% RH ± 5% RH	6 months	minimum four time points (e.g. 0/6/9/12)
Freezer Storage			
Long-term	-20°C ± 5°C	12 months	each 3rd month 1st year, each 6th month 2nd year, annually thereafter
Drug substances intended for storage below	-20°C		treated case-by-case

Test conditions for stability studies according to ICH Q1A (R2) for new drug products and new drug substances

For long-term studies, it is up to the manufacturer whether the tests are carried out at 25 ± 2°C/60% RH ± 5% RH or at 30°C ± 2°C/65% RH ± 5% RH. If the long-term conditions are 30°C ± 2°C/65% RH ± 5% RH, there are no tests under intermediate conditions.

For semi-permeable pharmaceutical containers such as bags or bottles and ampoules without moisture barrier, special test conditions with reduced moisture content apply. In this case, the fluid loss is an additional test parameter.

3. GMP-compliant design of climate chambers

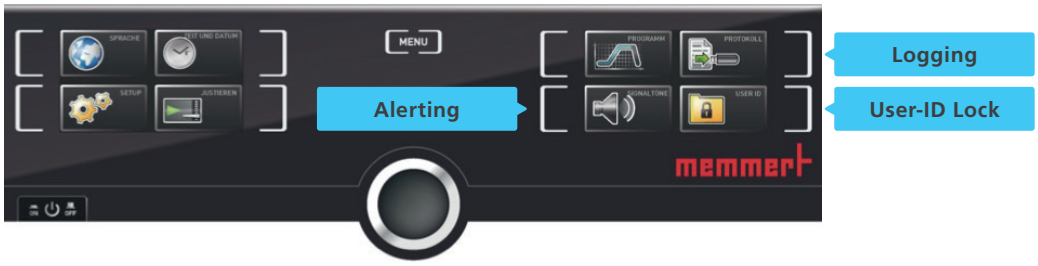
3.1. Long-term precision

Stability samples are often placed for several years under defined temperature and humidity conditions in a climate chamber. On an industrial scale, climate rooms and climate chambers are also in use. Reliability, especially with regard to fail-safety, precision and long-term stability as well as high-precision reproducibility, must be guaranteed at all times.

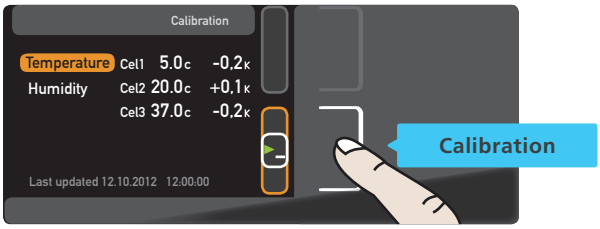
As part of the equipment for stability testing, climate chambers must be continuously maintained and qualified in accordance with GMP. The relevant technical functions as well as the constancy and homogeneity of temperature and humidity are tested. The qualification proves and documents that appliances and systems work reproducibly within the specified limits for temperature and humidity in the entire intended work area. Under Guideline ICH Q1A (R2), the maximum deviation for relative humidity is ± 5%, for temperature ± 2°C. To ensure that the test conditions are maintained, the climate chamber must be connected to an alarm system and the internal sensors must be calibrated via the control system.

3.2. The most important requirements for a climate chamber

Precise maintenance of temperature and humidity via suitable sensors
Simulation of all climate zones for stress tests, accelerated, intermediate and long-term and ongoing studies worldwide
Chamber with internal sensors to be calibrated
Manipulation safe data logging of temperature and humidity
Software to meet the requirements for the use of electronically stored data sets and electronic signatures as laid down in regulation 21 CFR Part 11 of GMP / US Food and Drug Administration
Lock functions and lockable door
Alert system (visual and acoustic alarm, also via central alerting systems)
Multiple overtemperature protection and protection against over-/underhumidity
Logging and documentation of all important parameters such as date and time, preset/actual temperature, preset/actual humidity, (light)
Network capable
Potential-free contacts for connecting external measuring instruments and sensors
Easy to clean
Plenty of usable space with little space requirement
Low power consumption



GMP-compliant functions of a climate chamber (©Memmert)



GMP-compliant calibration of temperature and humidity sensors (©Memmert)

4. Examples of stability and climate tests in other industries

Stability tests are also common and sometimes mandatory in other industries outside pharmaceutical research and manufacture.

4.1. Climate testing of food packaging

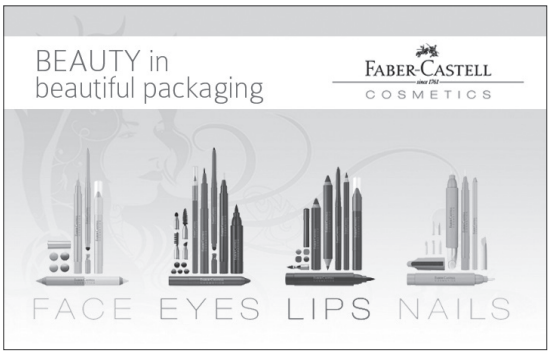
A can is not just a can, at least according to Hoffmann Neopac, the Swiss specialist in pocket packs made of metal or metal and plastic. Long-lasting quality is the top priority for every product innovation, which is why the metal cans are put through their paces in an HPP constant climate chamber.

Temperature-humidity pairings of 40°C/80% RH alternating with 25°C/40% RH are commonly used. Depending on the requirements, the tests take place in a constant climate and/or in an alternating climate (based on the climate tests according to DIN EN ISO 6270-2) and last between one day and several months.

Detailed report:
www.atmosafe.net/en/climate-testing/metal-containers

4.2. Storage tests for decorative cosmetics

As a partner of internationally renowned cosmetic companies, Faber-Castell Cosmetics is one of the leading private label manufacturers of high-quality cosmetic pencils for face, eyes, lips and nails. Sophisticated formulations and packaging are developed and tested to turn future cosmetic trends into successful products. The company uses a cooled incubator for storage tests to reliably assess the quality of new developments.

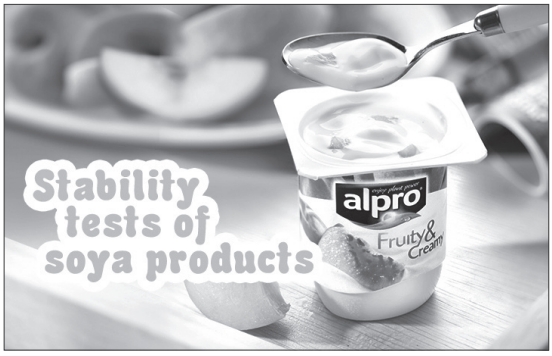


The wooden and plastic-cased cosmetic pencils and applicators are stored in the cooled incubator for twelve weeks at different temperatures in the range from 5°C to 50°C and then tested for changes to the lead or sleeve. In addition, the cooled incubator is used for temperature tests at changing temperatures.

Detailed report:
www.atmosafe.net/en/storage-tests/decorative-cosmetics

4.3. Stability testing of soya products

More and more people are turning to purely vegetable products such as soya drinks, soya desserts and yoghurt alternatives. Before delivery, all Alpro brand products are subject to strict quality controls and microbiological tests.



Accelerated testing: Samples of ultra-high temperature products from production are exposed to elevated temperatures of +30°C to +55°C in a heating oven. After 3 and 5 days the pH value is determined and various tests for spores are carried out. Cultivation of fresh samples: The fresh product samples applied to Petri dishes are incubated in a refrigerated incubator at +25°C. After alternatively 3 or 5 days, the pH value is determined again and microbiological tests are carried out.

Detailed report:
www.atmosafe.net/en/stability-testing/soya-products

4.4. Shelf life testing of dairy products

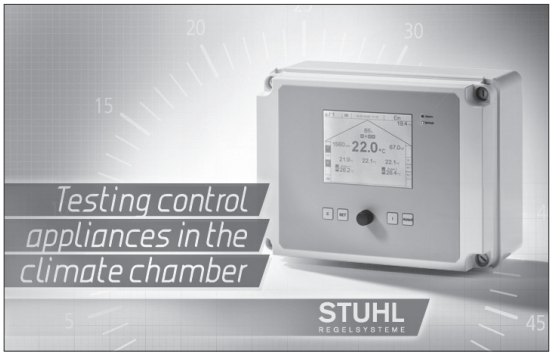
Bright Food, the parent company of Bright Dairy & Food, is one of the largest food companies in China. In addition to expanding production capacities for milk, yoghurt, ice cream, cheese and other dairy products, high product quality is a declared goal of the company

The food safety team at Bright Dairy & Food uses a Peltier-cooled incubator for microbiological investigations and durability tests. The microbiological test for fungal colonies is carried out at 20°C and lasts between 3 and 5 days. During shelf life testing, on the contrary, the microbiological status of a product is continuously monitored during its entire shelf life. In this case, the test duration and the temperature in the cooled incubator vary from sample to sample.

Detailed report:
www.atmosafe.net/en/incubating-and-breeding/dairy-products

4.5. Climate testing of control devices

The precision and reaction time with which sensors react to changes in ambient conditions make all the difference both in a control unit for building services engineering and in a temperature control cabinet. For this reason, Stuhl Regelsysteme GmbH from the Bavarian town of Spalt tests the functionality of its components in a climate chamber. The test specimens receive their signals in the climate chamber via a cable bushing. Signals as well as the test parameters temperature, humidity and test duration are recorded by external, calibrated measuring instruments. In parallel, the chamber-internal log of temperature and humidity is used for the plausibility check of the external measurement results. The control devices are exposed to constant temperature-humidity combinations as well as to climatic processes, with the test duration ranging from a few hours to 14 days.



Detailed report:
www.atmosafe.net/en/climate-testing/electronic-control-appliances

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Now in its third generation, Memmert has been developing and producing heating and drying ovens, incubators, climate chambers as well as water- and oilbaths at two locations in southern Germany (Schwabach and Buechenbach) for a very wide range of applications. Around 450 employees from about 30 nations are involved in the success of our company. In over 190 countries all over the world, hundreds of thousands of Memmert products have been permanently in use for decades. Therefore Memmert is one of the most innovative and leading manufacturers of temperature control devices worldwide.

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