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Product Stability

GENERAL VIEW ON PRODUCT STABILITY

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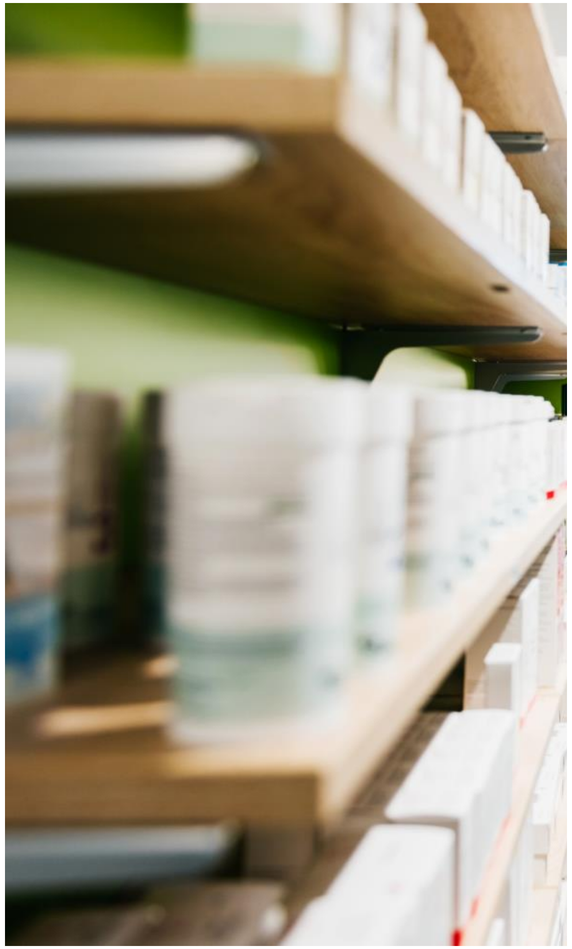
Stability Testing



What is stability testing?

Stability testing is a process where a set of tests are used to provide **evidence on how the quality** of a drug substance/product **varies with time** under the **influence** of a variety of **environmental factors** such as temperature, humidity, and light. Stability tests are also used to **establish** a **re-test period** (drug substance) or a **shelf life** (drug product) and **recommended storage conditions**.

Why stability testing?

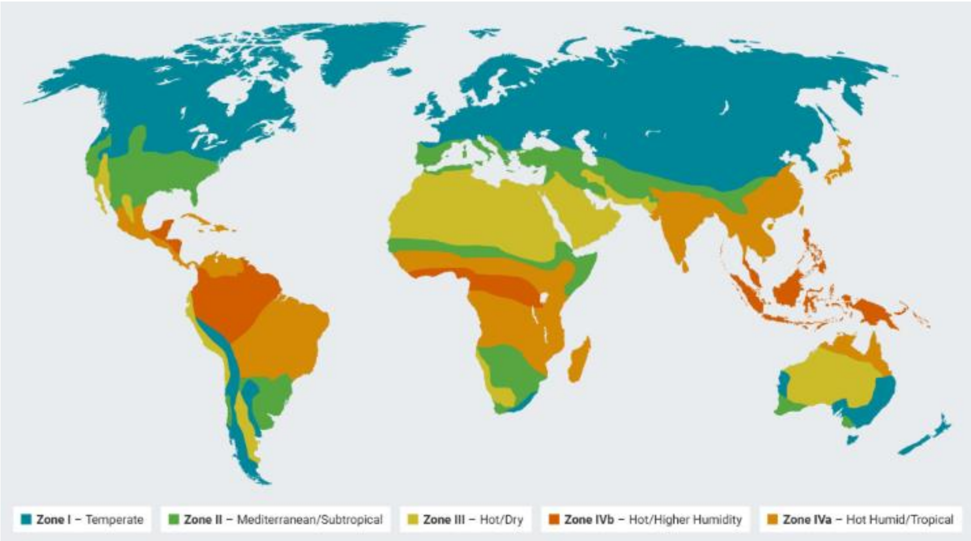
Stability testing is not only important to **establish** a **re-test period** (drug substance) or **shelf life** (drug product) and **appropriate storage conditions**. It is also **crucial** because it allows manufacturers to **monitor the quality** of the products ensuring that they **stay within specification** while on the market **thus being safe for the patient**.

Stability Testing

What are the stability test conditions based on?

The test conditions are based on the effect of the **climatic conditions** that are, for stability testing purposes, divided in **4 different climatic zones** according to what W. Grimm described in *Drugs Made in Germany.*

Climatic Zone	Description	Environmental Factors		Color on the Map
		Temperature (°C)	Humidity (%RH)	
I	Temperate climate	21	45	
II	Mediterranean and subtropical climate	25	60	
III	Hot and dry climate	30	35	
IVa	Hot and humid climate	30	65	
IVb			75	



Storage Conditions

What are the storage conditions for stability testing?

- The **storage conditions** should be appropriate to test **thermal stability** and, if applicable, **product sensitivity to moisture** or **potential for solvent loss**.
- The **storage conditions** and the **lengths of studies** chosen should be sufficient to cover **storage**, **shipment**, and **subsequent use**.
- There are 3 main types of storage conditions, **long term**, **intermediate** and **accelerated**.
- The table presents the **general conditions**, that should be **adjusted to the substance/product**.

	Types of Storage Conditions	Storage Condition	Minimum Time Period Covered
Climatic Zone I/II	**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
Climatic Zone III/IV	**Long term*****	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 or 12 months
	Intermediate**	30 °C ± 2 °C/65% RH ± 5% RH	6 months
	Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide between the two conditions. **If 30 °C ± 2 °C/65% or 75% RH ± 5% RH is the long-term condition, there is no intermediate condition. *** The storage conditions used for the long-term stability studies are determined by the climatic zone in which the product is intended to be marketed.

Testing Frequency

- The drug products/substances can be tested through **long term testing**, **intermediate testing** and **accelerated testing**.

Long Term Testing

- What is it?

  Stability studies under the **recommended storage condition** for the **re-test period** (drug substance) or **shelf life** (drug product) proposed for labeling.

- How does it work?
  - Minimum **time period** covered: **12 months**
  - **Time period** that should be covered: **intended shelf life**
  - **Frequency of study**:
    - Every **3 months** over the **1st year**
    - Every **6 months** over the **2nd year**
    - **Annually thereafter**

Testing Frequency

- The drug products/substances can be tested through **long term testing**, **intermediate testing** and **accelerated testing**

Accelerated Testing

- What is it?

  Studies designed to **increase the rate of chemical degradation** or **physical change** of a drug substance/product by using **exaggerated storage conditions.**

- What is it used for?

  Data from these studies can be used to assess **longer term chemical effects** at non-accelerated conditions and to **evaluate the effect of short-term excursions.**

- How does it work?

  At least a **3-point study** that **includes the initial and final points**. For products that are likely to approach **significant change** criteria, adaptions on testing are necessary

  But what is **significant change**?

Testing Frequency

- **What is significant change?**

A **change** is **considered significant** if:

- There is a **5% change in the assay** comparing to its initial value or **failure to meet** the **potency acceptance criteria** when using biological or immunological procedures;
- There is one or more **degradation products above** the **acceptance criteria**;
- The drug product **fails** to meet the **acceptance criteria** for:
    - **physical attributes**, **appearance** and **functionality tests** (like hardness or phase separation), unless expected;
    - **pH** (if appropriate for the dosage form);
    - **Dissolution** for 12 dosage units (if appropriate for the dosage form).

Testing Frequency

- The drug products/substances can be tested through **long term testing**, **intermediate testing** and **accelerated testing**.

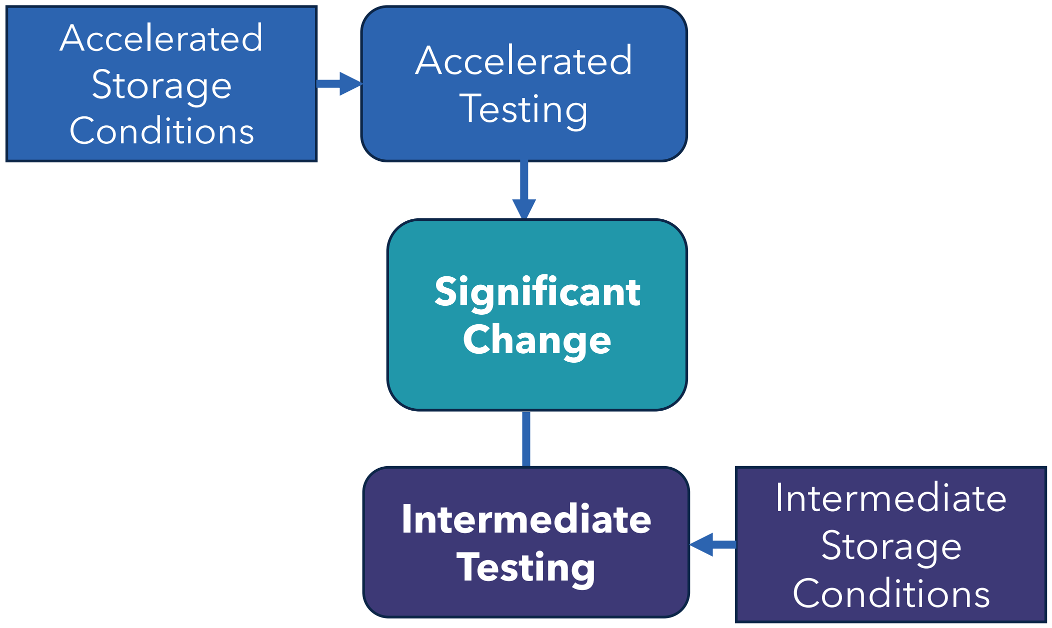
Intermediate Testing

- What is it?

  Studies designed to **moderately increase** the rate of **chemical degradation** or **physical changes** for a drug substance/product.

- How does it work?

  It is recommended a **minimum of 4 time points, including the initial and final time points**.



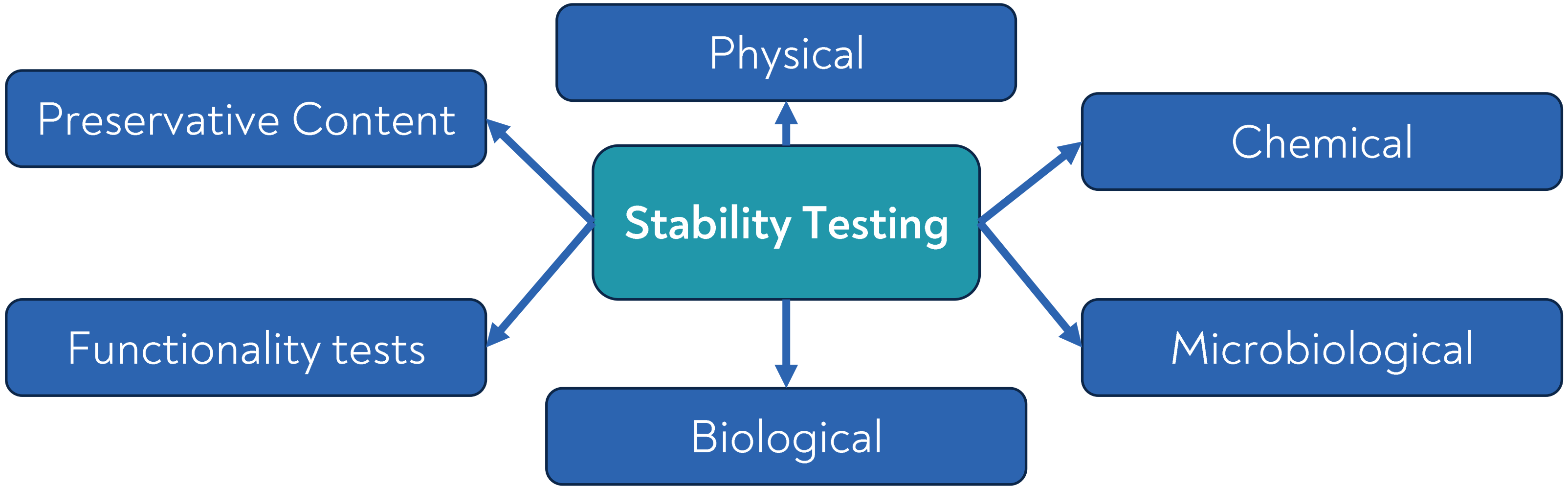
Types of Stability Tests

- **Stress Testing**
  - Tests used to help identify **likely degradation products**. The type of test performed depends on the drug substance/product involved.
  - Stress testing should include the effects from **temperature**, **humidity** and **pH** variations. **Photostability** testing should also be included.
- **Testing of the Container Closure System**
  - Test to ensure the **endurance** of the drug substance/product **package** proposed for storage and distribution.

Types of Stability Tests

Specification Tests

- The specification tests are a **list of tests**, reference to **analytical procedures** with certain **acceptance criteria**. These tests are addressed in ICH Q6A and Q6B. Specifications for degradation products in a drug substance are discussed in ICH Q3A.
- Stability studies should test the **attributes** that are **susceptible to change** during storage and likely to **influence quality**, **safety**, and/or **efficacy**.

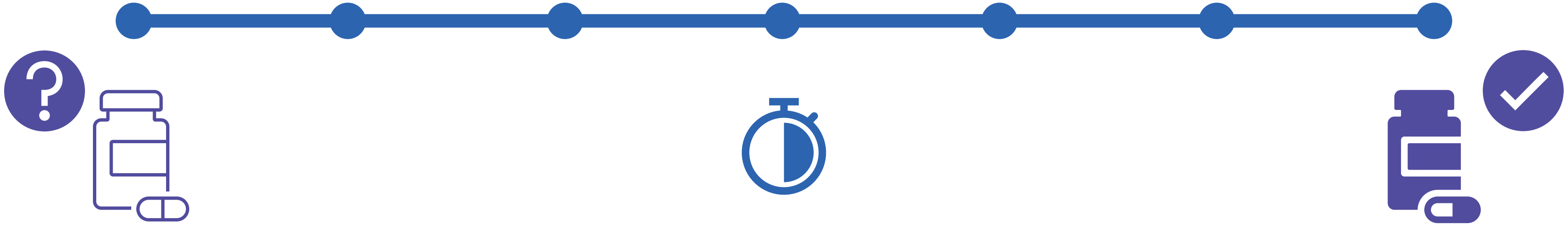


Shelf Life

- The **shelf life**, also referred to as expiration dating period, is the **time period** in which a **drug product** is **expected to remain** within the **approved specifications**, if **stored** under the **conditions defined** on the label.

What are the studies needed to establish drug product shelf life ?

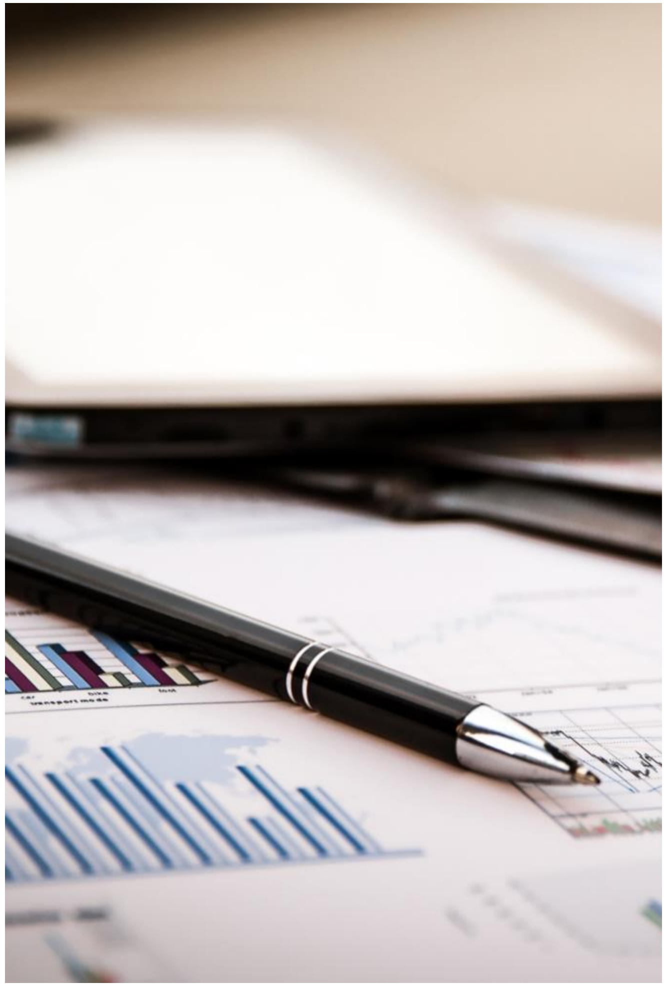
- The shelf life proposed by manufacturers is established by taking into consideration all available stability information. **Long term stability studies** should be conducted to **at least 3 batches** of the drug product **to establish a shelf life**.
- If the studies don't cover the above, at the time of submission, an additional commitment should be made. This commitment should include a **long-term stability study of 3 batches**, as well as a **6 months accelerated study**.



Shelf Life

- **How do manufactures establish drug product shelf life?**

  - Manufacturers propose shelf lives using a **mathematical extrapolation** and a **statistical analysis** of all data resulting from the stability studies preformed.
  - To analyze a **quantitative attribute** that is **expected to change** with time it is possible to determine the time at which the 95 one-sided confidence limit for the mean curve intersects the acceptance criterion. These **Statistical methods** should be employed to test the **goodness of fit** on all batches and combined batches to the degradation curve.
  - Any evaluation should consider not only the **assay** but also the **degradation products** and other **appropriate attributes**.



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- Graduate and master's degree in chemical and biochemical engineering at Nova School of Science and Technology in Lisbon and at Sorbonne Université in Paris.
- More than one year experience in the pharmaceutical industry, more specifically in R&D, with solid and semisolid formulations.
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