Packaging Materials and Closures in Terms of Stability

In accordance with the methods of use and administration of medicinal products, packaging materials, closures and containers vary a great deal and have to meet a wide variety of different requirements.

To ensure the efficacy of a product during its total shelf-life, pharmaceuticals must be regarded as a combination of the medicinal product itself and the packaging.

Types of the most commonly used packaging materials are;

- Glass
- Plastic
- Metal

- **Glass**

For a large number of pharmaceuticals, including medicinal products for oral and local administration, glass containers are usually the first choice (e.g. bottles for tablets, injection syringes for unit- or multidose administration). Different types of glass may be necessary, depending on the characteristics and the intended use of the medicinal products concerned.

Manufacturers should arrange with their suppliers to obtain the appropriate type of glass container for the intended use. Suppliers should provide the raw and packaging materials in conformity with industrial norms. Classifications of types of glass are given in the European and United States pharmacopoeias, whereas no such classification exists in the Japanese pharmacopoeia.

Glass can be tested for light transmission and hydrolytic resistance. In the Japanese pharmacopoeia, such tests are described only for glass containers for injection, whereas in the European and United States pharmacopoeias they are given for all types of glass containers.

- **Plastics**

Some containers are now being made of plastics; the main use is for bags for parenteral solutions. Plastic containers have several advantages compared with glass containers:

— they are unbreakable

— they are collapsible

— they are light.

The European, Japanese and United States pharmacopoeias all describe materials of the same type, but there are considerable differences in the classification and presentation.

As far as tests are concerned, the three pharmacopoeias are extremely difficult to compare. The European pharmacopoeia is the most detailed and requires tests in relation to the use and routes of administration of the medicinal product. Moreover, the same concept is extended to bulk containers for active ingredients.

- **Metal**

Metal containers are used solely for medicinal products for nonparenteral administration. They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders. Aluminium and stainless steel are the metals of choice for both primary and secondary packaging for medicinal products. They have certain advantages and provide excellent tamper-evident containers.

Since metal is strong, impermeable to gases and shatterproof, it is the ideal packaging material for pressurized containers.

Descriptions and tests can be found in the norms and standards of the ISO; these have been established in collaboration with manufacturers.

Requirements are not given in pharmacopoeias; the suitability of a particular material for a container is normally established by conducting stability studies in which the material is in contact with the drug in question.

Closures

- Closures used for the purpose of covering drug containers after the filling process should be as inert as possible. They should not give rise to undesired interactions between the contents and the outside environment, and should provide a complete seal. Besides their protective function, closures must also allow the easy and safe administration of the drug.
- Depending on the application, closures may have to be pierced with a needle for intravenous sets. Such closures are made from elastomeric materials (rubbers), while those that cannot be pierced are generally made from plastics such as polyethylene or polypropylene.

- ✓ Depending on the type of container, closures may have different shapes and sizes, e.g. stoppers for infusion or injection bottles or plungers for prefilled syringes. A special design of stopper may also be required for some pharmaceutical production processes such as lyophilization.
- ✓ For parenteral preparations, the combination of glass containers and elastomeric closures, usually secured by an aluminium cap, is widely used. Typical examples are infusion bottles, injection vials and prefilled syringes. The rubber closures used within such a system must be carefully selected in accordance with the intended purpose. Most often, improper rubber closures are the cause of incompatibility between the packaging and the drug.

The major types of the closures are;

- Rubber closures
- Caps or overseals
- Special types of closure

• Rubber closures

Rubber consists of several ingredients, one of which is elastomer. Modern rubber compounds used in packaging pharmaceuticals contain only a limited number of ingredients, which are very difficult to extract. Closures made from such materials generally do not pose any problems, and can be used in contact with a large number of drug preparations.

- ✓ **Rubber closures for pharmaceutical use must meet the relevant requirements of the most important pharmacopoeias (the European, Japanese and United States pharmacopoeias). International standards have also been established (ISO 8871). It should be emphasized that the requirements of pharmacopoeias and standards must be seen as minimal requirements. The suitability of a rubber closure for a given application can only be established by means of stability studies.**

- **Caps or overseals**

Caps or overseals are used to secure the rubber closure to the container in order to maintain the integrity of the seal under normal conditions of transport, handling and storage during the intended shelf-life of the product. Such caps are usually made of aluminium and can be equipped with a plastic top to facilitate opening. Caps also provide evidence of tampering: once opened or removed they cannot be repositioned. This is especially true for caps with a plastic top.

- **Special types of closure**

Demographic trends are causing new problems for packaging designers.

Thus while child-resistant closures safeguard children against drug intoxication, opening such packaging may prove difficult for the increasing number of elderly persons in the population.

In this context, special closure systems developed for different age groups are as follows:

- **tamper-evident closures,**
- **child-resistant closures.**

- **Tamper-evident closures:**

- **Tampering includes three aspects, namely altering, pilfering and falsifying the pharmaceutical product. To prevent tragic accidents and especially malicious tampering, manufacturers try to create safe packaging and governments continue to update regulations to include new tamper-evident technology.**
- **The concept of tamper-evident packaging is found in the United States pharmacopoeia, which stipulate that all OTC drugs must comply with the tamper-evident packaging and labelling requirements of the FDA, unless specifically exempted. Products covered by the regulation include all OTC drugs, toothpaste and topical dermatological products, oral cosmetic liquids, contact lens solutions and tablets.**

- ✓ The Food and Drug Administration (FDA) listed 11 Technologies capable of satisfying the definition of tamper-evident packaging, while a twelfth was added for sealed cartons. The list includes film wrappers, blister packs, bubble packs, heat-shrunk bands or wrappers, paper foil or plastic packs, bottles with inner mouth seals, tape seals, breakable cap-ring systems, sealed tubes or plastic blindend heat-sealed tubes, sealed cartons, aerosol containers and all metal and composite cans.

- **Child-resistant closures:**

- Tragic accidents involving the drug intoxication of children has led to new legislation making it difficult for drug packaging to be opened by young children, while allowing adults easy access. Such packaging is designated as child-resistant.
- The three most common reclosable child-resistant types of closure are the “press–turn”, the “squeeze–turn” and a combination lock.
- Most designs that are child-resistant require two hands to open the closure. Such packaging can cause problems for elderly people, and can even lead to the deliberate purchase of drugs with packaging that is not child-resistant; alternatively, the child-resistant closure may not be replaced on the container.

Stability Tests

Stability is one of the indicators that a drug is effective, safe and quality.

It is important both for the quality of the drug and from the economic point of view, to prove the stability of the drug produced by the manufacturer pharmaceutical company.

Why are Stability Tests Done?

✓Stability tests are carried out to determine, guarantee and prove that the active substance and the product remain chemical, physical, therapeutic and toxicological stability until the end of shelf life.

✓ These tests are performed to determine the shelf life and life cycle of an active substance or pharmaceutical product in its packaging and storage conditions.

World Climatic Zones

In terms of stability studies, the world is divided into 4 climatic zones. The main approaches involved in this distinction are ”Mean Kinetic Temperature“ and «Average Relative Humidity»

The mean kinetic temperature can be expressed as:

$$T_K = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{t_1 e^{\left(\frac{-\Delta H}{R T_1}\right)} + t_2 e^{\left(\frac{-\Delta H}{R T_2}\right)} + \cdots + t_n e^{\left(\frac{-\Delta H}{R T_n}\right)}}{t_1 + t_2 + \cdots + t_n}\right)}$$

Where:

T_K is the mean kinetic temperature in kelvins
ΔH is the activation energy (typically within 60–100 kJ·mol^{-1} for solids or liquids)
R is the gas constant
T_1 to T_n are the temperatures at each of the sample points in kelvins
t_1 to t_n are time intervals at each of the sample points

When the temperature readings are taken at the same interval (i.e., $t_1 = t_2 = \ldots = t_n$), the above equation is reduced to:

$$T_K = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{e^{\left(\frac{-\Delta H}{R T_1}\right)} + e^{\left(\frac{-\Delta H}{R T_2}\right)} + \cdots + e^{\left(\frac{-\Delta H}{R T_n}\right)}}{n}\right)}$$

Where:

n is the number of temperature sample points

World Climatic Zones

CLIMATIC ZONE	DEFINITION	STORAGE CONDITIONS
I	TEMPERATE CLIMATE	21°C/45 % R.H
II	SUBTROPICAL AND MEDITERRANEAN CLIMATE	25°C/60 % R.H
III	HOT , DRY CLIMATE	30°C/35 % R.H
IV	HOT , HUMID CLIMATE	30°C / 70% R.H

World Climatic Zones	Mean Kinetic Temperature (°C)	Average Relative Humidity (%)
I. Zone: TEMPERATE (England, Russia, Northern Europe, Canada)	21 ± 2	45 ± 5
II. Zone: MEDITERRANEAN (USA, Japon, Southern Europe, Turkey)	25 ± 2	60 ± 5
III. Zone: HOT, DRY (Iran, Iraq, Sudan)	30 ± 2	35 ± 5
IV. Zone: HOT, HUMID (Brazil, Ghana, Indonesia, Philippines)	30 ± 2	70 ± 5

Storage Temperatures Used in Stability Tests:

The terms used to indicate storage conditions in pharmaceutical packaging are as follows:

Room Temperature: It is the temperature between 20-25 °C depending on climate zones. The permissible limits are 15-30 °C. for Turkey is 25 °C.

Cool Location: Specifies the temperature between 8-15 °C. A refrigerator can also be used for this temperature.

Cold (Refrigerator): Indicates the temperature between 2-8 °C.

Deep Freezer: Indicates the temperature between (-25) - (-10) °C.

Types of Stability Test:

- ✓ Isothermal Tests
- ✓ Non Isothermal Tests

A) Isothermal Stability Tests:

These tests are legally required to determine the shelf life of a drug. In these tests, the temperature is kept constant throughout the test. It is divided into 3 groups.

➢ Long Term Stability Tests:

It is the legal tests that must be done in order to obtain a license. These tests are carried out during the prescribed shelf life in conditions of temperature and humidity given the condition of storage on the label of the drug. These tests are carried out to determine the stability of both the active substance and the drugs under storage and ambient conditions. From these tests, the re-test period for the active substance and the shelf-life for final product are determined. The conditions of these tests are often chosen to reflect the ambient conditions in which the active substance and the drug will be kept and stored.

➢ Accelerated Stability Tests

These tests are part of the stability testing program that should be done legally. Tests carried out to increase the rate of chemical decomposition and physical change in the active substance and final product by applying accelerated test conditions such as high temperature and high humidity.

Accelerated stability tests, can be used to determine the temporary shelf-life and the short-term exposure to conditions outside the storage conditions specified on the product's label during transport. However, accelerated stability tests should always be completed with real-time long-term stability tests under the expected storage conditions.

➢ Stress Tests (Forced-Degradation Tests)

Specifically, these tests are carried out during drug development to reveal the specific stability of the active substance.

The effects of high temperature, humidity, light, oxidant agents and pH range on stability are investigated by stress tests.

These tests are carried out to obtain information about the degradation products and the degradation mechanisms of the active substance under forcible conditions.

According to the International Conference of Harmonization (ICH), stress tests are performed at temperatures of at least 10 ° C higher than accelerated tests, or at high humidity conditions (75% relative humidity or more).

In stress tests, high temperatures of 50 C, 60 C, 70 C, 80 C and 90 C are applied as test temperatures.

How are Stability Tests Applied?

Isothermal stability tests are carried out in the following stages:

1. Tests on the active substance (Stress tests):

These are the first tests performed by the company that produces the active substance. Under the influence of factors such as very high temperature and very high humidity, re-testing of the active substance is made in order to determine the degredation mechanisms, to determine the degredation products and to determine the stability criteria for preparation of the dosage forms.

ICH GUIDELINES	TITLE
Q 1 A	Stability testing of new drug substances and products (second revision)
Q1B	Stability testing : photo stability testing of new drug substance and products.
Q1C	Stability testing for new dosage forms
Q1D	Bracketing and matrixing designs for stability testing of drug substances and products
Q1E	Evaluation of stability data

- accelerated temp
  - 6 mons study at 40°C with 75% relative humidity

Stress Testing

- May be carried out on a single batch of the drug substance. Should include the effect of temperature, humidity, oxidation and photostability.
  - For example the effect of temperatures in 10 degrees increments above that for accelerated testing (e.g. 50°C to 60).
- The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of PH values when in solution or suspension.
- Helps to identify the degradation products, therefore the degradation pathways and the intrinsic stability of the molecule, and validate the stability indicating power of the analytical procedures used.
- Photostability is taken into account as described in ICH Q1B.

Why are stress tests performed?

- Determination of chemical degradation mechanisms of active substance,
- Definition of degradation products,
- Demonstration of intrinsink stability of the molecule,
- Contributing to the validation of analytical methods,
- Formulation of the dosage form and its guidance in the determination of pharmaceutical procedures,
- Having a router in the selection of packaging material (for the active substance and dosage form).

The stability test conditions for the active substances and final dosage forms according to the ICH stability climate zones are as follows:

ICH 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

Long Term Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum 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

Accelerated and Intermediate Testing Conditions

Climatic Zone	*Temperature*	*Humidity*	*Minimum 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*

If there is a significant stability problem in the accelerated test environment, the test is repeated for 1 year in 30°C ± 2°C / 60 ± 5% relative humidity.

The most important stability problem that can be observed here is that the properties of the active substance go beyond the specifications.

2. Accelerated and long-term tests on the active substance

3. Tests carried out during formulation development:

After examining the stability properties of the active substance, stability experiments are performed in 3 ways to develop the formulation.

- ✓ Effect of excipients on stability
- ✓ Effect of the production method on stability
- ✓ Effect of packaging on stability

4. Final product tests

Long-term and accelerated tests are carried out on the final product. If a significant stability problem is observed in the accelerated test environment, the test shall be carried out. 30°C ± 2°C and 60 ± 5% relative humidity is repeated for 1 year as same as active molecule.

Important stability problems are:

- 5% active substance loss within 6 months,
- At least one of the degradation products is out of the specified limits,
- Changes in physical properties (color, appearance, taste, phase separation, hardness, cakes etc.)
- pH outside the pre-determined limits,
- The dissolution rate does not meet the acceptance criteria in 12 dosage units.

Test Ranges of Stability Tests

The test intervals of the samples taken during the tests should be at a frequency that reflects the stability characteristics of the dosage forms.

Recommended sample frequency:

- First year every 3 months (3rd, 6th, 9th and 12th months)
- Second year every 6 months (18th and 24th months)
- Then once a year (at 36th, 48th and 60th months)

Bracket and Matrix Design for Stability Tests

These designs are done to reduce the stability tests cost.

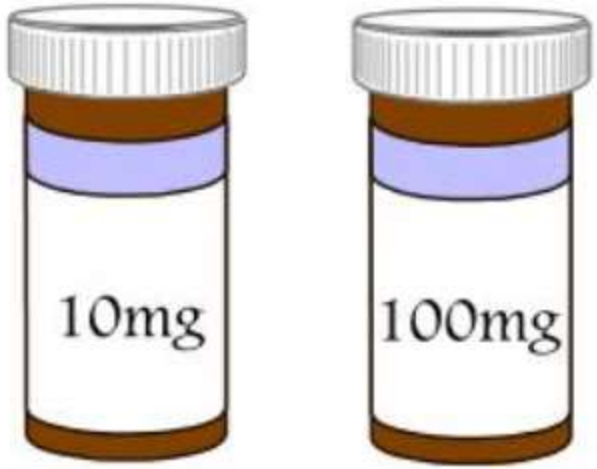
If there is more than one dose of a finished product and a different package size or shape, these two different designs can be made to reduce the stability tests performed at all time points.

Bracket Design

This design is the most appropriate alternative stability design to ensure that stability tests in all test ranges are not performed if the product is in multiple doses and packaging size. Accordingly, samples at only the lower and upper ends of the test samples are tested at all points. In this way, it is assumed that the samples in the middle are tested.

Bracketing

Complete removal of some batches from testing



Example of a bracketing design

Strength		50mg			75mg			100mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15ml	T	T	T				T	T	T
	100ml									
	500ml	T	T	T				T	T	T

T = Sample is tested

Matrix Design

If many factors (different series, doses, vessel sizes) are to be tested in the product's stability tests, all stability is performed as an alternative to the test design. According to the design, it is assumed that each set of samples tested at specific time intervals represents all samples.

Matrixing

Removal of some testing from all batches

Example of a matrix design

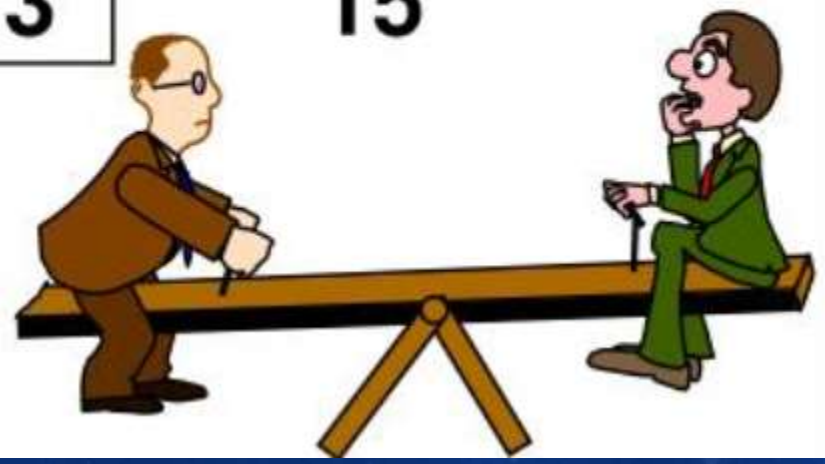
- **MATRIXING - Simple design on time points:**
  - A practical, "one-half reduction":

Time point (months)		0	3	6	9	12	18	24	36
Strength 1	Batch 1	T	T		T	T		T	T
	Batch 2	T	T		T	T	T		T
	Batch 3	T		T		T		T	T
Strength 2	Batch 1	T		T		T		T	T
	Batch 2	T	T		T	T	T		T
	Batch 3	T		T		T		T	T

T = sample tested

For one condition eg. 25 °C/60%RH and one presentation

Month:	0	3	6	9	12	18	24	36	Totals
Batch 1	X	X			X		X	X	5
Batch 2	X		X	X			X	X	5
Batch 3	X		X		X	X		X	5
Totals	3	1	2	1	2	1	2	3	15



A balanced matrix

B) Non-Isothermal Stability Tests:

Tests where the temperature is changed over the stability run time. These tests can be used to obtain results in a short time during the formulation development phase, but are not official tests. Although these tests were easier and shorter than isothermal tests, their results were not as strong as isothermal tests.

These are generally tests that are suitable for liquid drug forms in the form of solutions or suspensions.

During these tests, the temperature is changed according to a specific program.

Various temperature programs have been developed for use in nonisothermal tests. These;

- Uncontrolled temperature programs
- Flexible temperature programs
- Cyclical temperature programs
- Linear temperature programs

Stability Test Protocol

Before the start of the stability tests, the test-related stability protocol is prepared. A properly prepared stability test protocol should include:

- For active substance or for finished product
- Storage conditions
- Sampling plan
- Test periods

- Test methods
- Validation of methods
- Properties and sources of active substances and excipients
- Size and number of test series
- Cap-cover type, size and number
- Test parameters
- Acceptance criteria

- Statistical evaluation
- Giving results
- Repeat time of results if necessary
- Determined shelf life

Specifications to be Examined in Stability Tests

Specification; is a set of properties that covers tests, references to analytical methods, and admission criteria (numerical limits for defined tests, spacing or other criteria).

Determines the criteria to show that it is acceptable for the desired use of an active substance or drug.

The conformity of the specification defines that an active substance or drug meets the established acceptance criteria when tested according to established analytical methods.

The specifications are the critical quality standards agreed by the manufacturer, proposed and accepted by the official authorities.

PATENT

8TH WEEK

Patent as a medical definition; It is a document that exceeds the known state of the art and provides the protection of industrially applicable inventions for 20 years.

Patent as a legal definition; it is a packaged non-prescription drug which is protected by a trademark and whose contents are incompletely disclosed.

Patentability Conditions

- Novelty
- Inventive step
- Industrial applicability

ADVANTAGES OF PATENS

- A patent gives you the right to stop others from copying, manufacturing, selling or importing your invention without your permission.
- You get protection for a pre-determined period, allowing you to keep competitors at bay.
- You can then use your invention yourself.
- Alternatively, you can license your patent for others to use it or you can sell it. This can provide an important source of revenue for your business. Indeed, some businesses exist solely to collect the royalties from a patent they have licensed.

DISADVANTAGES OF PATENS

- Your patent application means making certain technical information about your invention publicly available. It might be that keeping your invention secret may keep competitors at bay more effectively.
- Applying for a patent can be a very time-consuming and lengthy process (typically three to four years) - markets may change or technology may overtake your invention by the time you get a patent.

- Cost - it will cost you money whether you are successful or not - the application, searches for existing patents and a patent attorney's fees can all contribute to a reasonable outlay. The potential for making a profit should outweigh the time, effort and money it takes to get and maintain a patent.
- You'll need to remember to pay your annual fee or your patent will lapse.
- You'll need to be prepared to defend your patent. Taking action against an infringer can be very expensive. On the other hand, a patent can act as a deterrent, making defence unnecessary.

PATENT APPLICATION TYPES

- International Patent Application
- Regional Patent Applications
- National Patent Applications

PATENT TYPES IN DRUG

- Product Patent
- Formulation Patent
- Indication Patent
- Process Patent

- **Product Patent:** It is intended to protect the product itself. It is the most inventive type of invention. It is divided into four sub-categories.

  - Molecule patent
  - Derivative patent
  - Polymorph patent
  - Active ingredient mixture patent

- **Molecular Patents:** Patents related to a new molecule or active substance obtained from nature for any medical or veterinary purposes.
- **Derivative Patents:** Patents related to a new active substance, derived from any new or known molecule / molecules.
- **Polymorph (Crystal Form) Patent:** Patents related to a new crystal form (polymorph structure) of any new molecule.
- **Active Ingredient Mixing Patent:** It relates to the use of more than one known or active substances or derivatives as a mixture

- **Formulation Patent:** It is the patent for the production method used to convert the form of dosage form with various auxiliary substances to ensure the effect of any active substance.

- **Indication Patent:** It is the patent for the first medical use of an existing or previously patent-registered drug or active substance or molecule, or secondary medical use where there is any effect other than the existing effect of a known drug or active substance or molecule.

- **Proses Patent:** Patents related to the process (method, method, method) applied to produce or prepare any product, crystal form, derivative or active ingredient.

Protection of pharmaceutical patents in Turkey entered into force in 1995. However, «Patent Law» protection started legally as of January 1, 1999. This law covers only molecules that have been filed for patent after 1995. This does not protect the original drugs whose patent rights were registered before 1995.

DATA PRIVILEGE

- In order for a drug to be placed on the market, it must be approved, that is, licensed.

- For this, the effectiveness and safety of the drug must be proven by research data. Data exclusivity covers the protection of all research data submitted by the research pharmaceutical company to the Ministry of Health during the registration process.

- Today, in developed countries, the data is protected for a certain period of time so that data submitted to the competent authorities are not referenced by other companies and not disclosed, so as not to cause unfair competition.

- This practice is called "Data Privilege" in international law.