LECTURE 2

# GMP, WHO guidelines and stability of medicines. Packaging and labelling

How manufacturing rules, stability studies and the container–closure system together guarantee quality until the expiry date

**Standardisation of Medicines and Raw Materials**
Educational programme 6B10102 – Pharmacy · 4th year · Department of Fundamental Medicine, Al-Farabi Kazakh National University

OUTLINE

# Lecture plan

1. GMP: principles and international systems
2. Structure of GMP and the pharmaceutical quality system
3. Stability studies: ICH Q1A(R2) and climatic zones
4. Shelf-life estimation, stress and photostability testing
5. Primary packaging: materials and tests
6. Labelling of medicines in the EAEU and the RK

# Five principles behind every GMP rule

### People

Qualified, trained staff with defined responsibilities; hygiene; a qualified person releases batches

### Premises and equipment

Designed to minimise errors and cross-contamination; qualified and maintained

### Documentation

“If it is not written, it did not happen”: specifications, procedures, batch records

### Processes

Validated processes, controlled changes, in-process controls

### Materials

Approved suppliers, quarantine, testing of starting and packaging materials

### Quality system

Deviations, CAPA, complaints, recalls, self-inspection, management review

**Goal of GMP:** every batch is consistently produced and controlled to the quality standards appropriate to its intended use

# One philosophy, several rule books

| System | Main document | Notes |
|---|---|---|
| **WHO GMP** | WHO Technical Report Series, e.g. TRS 986 Annex 2 (main principles, 2014) | Basis for WHO prequalification and many national systems |
| **EU GMP** | EudraLex Volume 4: Part I (products), Part II (APIs), 19+ Annexes | Annex 1 (sterile products) revised in 2022, in force since Aug 2023 |
| **PIC/S** | PIC/S Guide to GMP PE 009 | Inspectorate cooperation; text equivalent to EU GMP |
| **USA** | 21 CFR Parts 210 and 211 (cGMP) | FDA; “current” GMP |
| **EAEU** | EEC Council Decision No. 77 of 3 Nov 2016 | Harmonised with EU GMP; applies in Kazakhstan |
| **ICH** | Q7 (GMP for APIs), Q9 (risk), Q10 (quality system) | Harmonised scientific guidelines |

# Nine chapters of GMP

### 1. Pharmaceutical quality system

Management responsibility, product quality review

### 2. Personnel

Qualification, training, hygiene

### 3. Premises and equipment

Design, zoning, qualification

### 4. Documentation

Specifications, procedures, records, data integrity

### 5. Production

Prevention of cross-contamination, validation

### 6. Quality control

Sampling, testing, OOS, stability programme

### 7. Outsourced activities

Contracts between giver and acceptor

### 8. Complaints and recalls

Investigation, recall procedure

### 9. Self-inspection

Regular internal audits

# The pharmaceutical quality system keeps improving

**1 Monitoring**

- Process performance and product quality
- Trends, product quality review

**2 CAPA**

- Root cause of deviations and complaints
- Corrective and preventive actions

**3 Change control**

- Every change assessed for risk
- Approved before implementation

**4 Management review**

- Top management evaluates the system
- Resources and priorities



**Quality risk management (ICH Q9):** risk = severity × probability (× detectability); tools: FMEA, HACCP, Ishikawa diagram, risk ranking



# Stability decides the expiry date: a medicine must meet its specification until the last day of its shelf life

Stability = the capacity of a product to remain within its specification under the influence of temperature, humidity and light over time

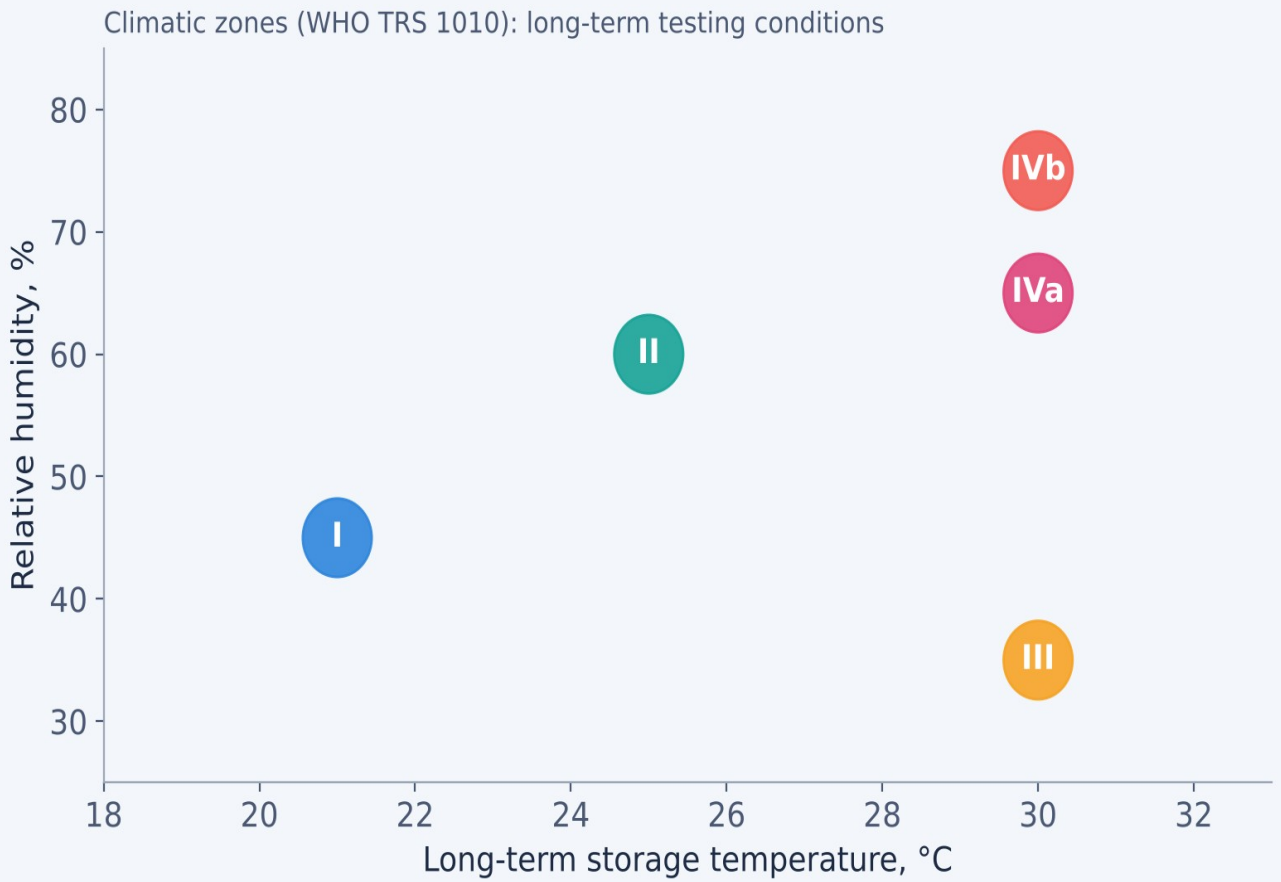
# Storage conditions for formal stability studies

| Study | Storage condition | Minimum period at submission |
|---|---|---|
| **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 |
| **Refrigerated product: long-term** | 5 °C ± 3 °C | 12 months |
| **Refrigerated product: accelerated** | 25 °C ± 2 °C / 60% RH ± 5% RH | 6 months |
| **Frozen product** | −20 °C ± 5 °C | 12 months |

### Study design

- **Batches:** at least 3 primary batches, at least 2 of pilot scale
- **Frequency:** every 3 months in year 1, every 6 months in year 2, then annually
- **Accelerated:** 0, 3 and 6 months
- **Package:** the proposed marketing container

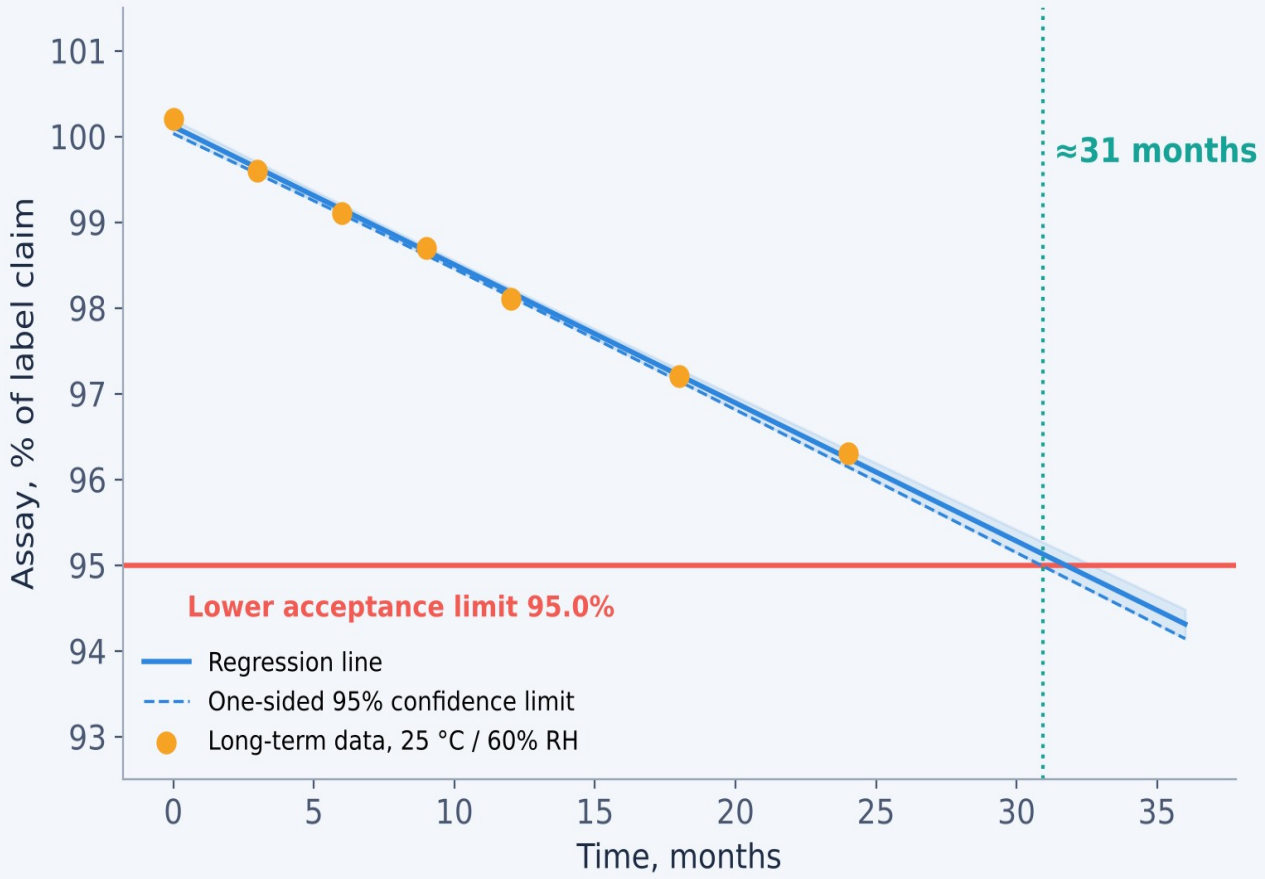
# The climate of the market defines the long-term condition




## Zones

- **Zone I** 21 °C / 45% RH: temperate
- **Zone II** 25 °C / 60% RH: subtropical, Mediterranean
- **Zone III** 30 °C / 35% RH: hot, dry
- **Zone IVa** 30 °C / 65% RH: hot, humid
- **Zone IVb** 30 °C / 75% RH: hot, very humid
- **EAEU:** long-term testing at 25 °C / 60% RH (zone II)

# Estimating shelf life from long-term data




## How to read the graph

- **Regression** of assay versus time for each batch
- **Shelf life:** time at which the one-sided 95% confidence limit meets the acceptance criterion
- **Here:** ≈ 31 months → proposed 30 months
- **Extrapolation:** up to 2 × the real-time period, but not more than 12 months beyond it
- **Significant change** at 40 °C: ≥ 5% loss of assay, a degradant above its limit, failure of appearance, pH or dissolution

# Forced degradation reveals how a molecule breaks

## Stress testing of the substance

- **Heat:** in 10 °C steps above accelerated
- **Humidity:** ≥ 75% RH
- **Hydrolysis:** acid, neutral, alkaline pH
- **Oxidation:** e.g. hydrogen peroxide
- **Purpose:** identify degradation pathways, prove the method is stability-indicating

## Photostability · ICH Q1B

- **Exposure:** not less than 1.2 million lux·hours of visible light
- **and** not less than 200 W·h/m² of near-UV energy
- **Sequence:** substance → product outside package → in immediate pack → in marketing pack
- **Result:** label “Protect from light” if needed

**Stability-indicating method:** separates the active substance from all its degradation products (specificity)

# The container is part of the medicine

### Glass type I

Borosilicate, high hydrolytic resistance: injections, infusions

### Glass type II

Soda-lime, surface-treated: acidic and neutral aqueous preparations

### Glass type III

Soda-lime: non-aqueous parenterals, oral liquids, powders

### Plastics

PE, PP, PET, PVC; tested for extractables and additives

### Blisters

PVC < PVC/PVDC < PVC/PCTFE < Alu–Alu: increasing moisture barrier

### Closures

Rubber stoppers, screw caps, child-resistant closures

### Tests

Hydrolytic resistance, light transmission, container closure integrity, leachables

### Secondary pack

Carton, leaflet; protects from light and damage, carries information

# What the label must tell

## Secondary (outer) package

- Trade name and INN
- Dosage form, strength, quantity in the pack
- Composition: active substances, excipients of known effect
- Route and method of administration
- Storage conditions, special warnings
- Batch number, expiry date
- Marketing authorisation holder, manufacturer, registration number

## Primary (immediate) package

- Small containers and blisters may carry reduced information
- Minimum: name, strength, batch, expiry date
- Marketing authorisation holder
- In Kazakhstan: information in the Kazakh and Russian languages
- Patient leaflet: approved text, same languages

**Why it matters:** labelling errors are a common reason for recalls; the label is checked at incoming control and at dispensing

# Key take-aways

1. **GMP** ensures consistent production; in Kazakhstan the EAEU GMP (Decision No. 77) applies
2. **ICH Q9 and Q10** add risk management and continuous improvement
3. **Stability studies (ICH Q1A, EAEU Decision No. 69)** use 25 °C/60% RH long-term and 40 °C/75% RH accelerated
4. **Shelf life** is set where the 95% confidence limit meets the acceptance criterion (ICH Q1E)
5. **Packaging and labelling** protect the medicine and inform the patient (Decision No. 76)

SELF-CHECK

# Control questions and literature

## Questions

1. Name the nine chapters of GMP Part I.
2. What are the four elements of the pharmaceutical quality system (ICH Q10)?
3. Give the long-term, intermediate and accelerated conditions of ICH Q1A(R2).
4. Which climatic zone applies to the EAEU and what are its conditions?
5. How is shelf life estimated according to ICH Q1E? What limits extrapolation?
6. What does “significant change” mean at accelerated conditions?
7. Compare glass types I, II and III and their uses.
8. List the mandatory items on the outer package of a medicine.

## Sources


- EEC Council Decision No. 77 (GMP), No. 76 (labelling), 03.11.2016
- EEC Collegium Decision No. 69 (stability), 2018
- ICH Q1A(R2), Q1B, Q1E, Q9(R1), Q10
- WHO TRS 986 Annex 2; TRS 1010 Annex 10
- EudraLex Vol. 4; Annex 1 (2022)
- European Pharmacopoeia, chapters 3.1–3.2