LECTURE 1

Quality assurance of medicines and general pharmacopoeial methods of analysis

Concepts of quality, the regulatory and technical documents that define it, and the general methods of the State Pharmacopoeia

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. Key terms: quality, QA, QC, specification
2. Life cycle of a medicine and quality systems
3. Regulatory framework of the RK and the EAEU
4. Normative documents and the structure of a monograph
5. General methods of analysis of the State Pharmacopoeia
6. Validation of analytical procedures (ICH Q2(R2))

KEY TERMS

Quality is built, assured and then verified

Quality of a medicine

The suitability of a medicine for its intended use, determined by identity, strength, purity and other characteristics

Quality assurance (QA)

A wide-ranging concept covering all matters that individually or collectively influence the quality of a product (WHO)

Quality control (QC)

The part of GMP concerned with sampling, specifications and testing, and with release procedures

Specification

A list of tests, references to analytical procedures and acceptance criteria to which a material must conform (ICH Q6A)

Standardisation

Establishing and applying uniform requirements for quality, written in normative documents

Batch (series)

A defined quantity of material produced in one process or series of processes, expected to be homogeneous

Remember: QC tests the product; QA designs the whole system so that the product is right first time

Quality is controlled at every stage of the life cycle

1 Development	Registration	Manufacture	Distribution	Pharmacy	Post-marketing
• Pharmaceutical development, QbD (ICH Q8) • Risk management (ICH Q9)	• Dossier in CTD format • Expert evaluation of quality, safety, efficacy	• GMP (EAEU Decision No. 77) • Pharmaceutical quality system (ICH Q10)	• GDP (EAEU Decision No. 80) • Cold chain, traceability	• Good pharmacy practice • Storage, dispensing, extemporaneous QC	• Pharmacovigilance (GVP) • Market surveillance, recalls

GxP chain: GLP → GCP → GMP → GDP → GPP → GVP; a weak link at any stage can make a medicine unsafe for the patient

Who sets the requirements in Kazakhstan and the EAEU

Level	Key documents and bodies	What they regulate
Law of the RK	Code of the RK “On public health and the healthcare system” (7 July 2020, No. 360-VI)	Circulation of medicines, registration, quality, state control
Regulator	Ministry of Health; Committee for Medical and Pharmaceutical Control; National Center for Expertise of Medicines and Medical Devices (NCEMMD)	Expertise, registration, inspections, quality testing
EAEU treaty	Agreement on common principles and rules for the circulation of medicines (23 Dec 2014)	Common market of medicines in the EAEU
EAEU rules	EEC Council Decisions No. 77 (GMP), No. 78 (registration), No. 80 (GDP), 3 Nov 2016	Manufacture, dossier and expertise, distribution
Pharmacopoeias	State Pharmacopoeia of the RK; Pharmacopoeia of the EAEU (EEC Collegium Decision No. 100, 11 Aug 2020); Ph. Eur., USP	General methods and quality standards
International	WHO guidelines, ICH guidelines (Q, S, E, M series), PIC/S	Harmonised scientific and GMP requirements

From pharmacopoeia to batch record

Public standards

- **State Pharmacopoeia RK,** Pharmacopoeia of the EAEU
- **General chapters:** methods of analysis
- **General monographs:** dosage forms, substances
- **Individual monographs:** a specific substance or product
- Mandatory for all manufacturers

Product documents

- **Normative document on quality** (registration dossier, Module 3)
- **Specification** of the manufacturer
- **Technological regulation** and batch record
- **SOPs** of the QC laboratory
- Approved for one product of one manufacturer

Batch documents

- **Certificate of analysis** (CoA) of a batch
- **Batch release** by the qualified person
- **Declaration / certificate** of conformity
- **Out-of-specification** investigation report
- Prove the quality of one batch

Structure of an individual monograph

Definition

Chemical name, formula, Mr, content limits (e.g. 99.0–101.0% on the dried substance)

Characters

Appearance, solubility; not requirements in themselves, but guidance

Identification

First and second identification: IR, TLC, reactions of ions and functional groups

Tests

Appearance of solution, pH, related substances, loss on drying, sulfated ash, elemental impurities

Assay

Titration, UV, HPLC: content of the active substance

Storage

Protected from light, airtight container, temperature

Labelling

What the label must state, e.g. content of water for hydrates

Impurities

List of specified impurities (A, B, C…) with structures

General methods of analysis: nine groups



2.1 Apparatus

Volumetric glassware, sieves, UV lamps



2.2 Physical and physicochemical

Melting point, refractometry, polarimetry, pH, IR, UV-Vis, TLC, GC, HPLC, CE, MS



2.3 Identification

Reactions of ions and functional groups



2.4 Limit tests

Chlorides, sulfates, iron, sulfated ash, residual solvents, elemental impurities



2.5 Assays

Water (Karl Fischer), nitrogen (Kjeldahl), oxygen flask, saponification value



2.6 Biological tests

Sterility, bacterial endotoxins, microbial enumeration



2.7 Biological assays

Potency of antibiotics, vaccines, hormones



2.8 Pharmacognosy

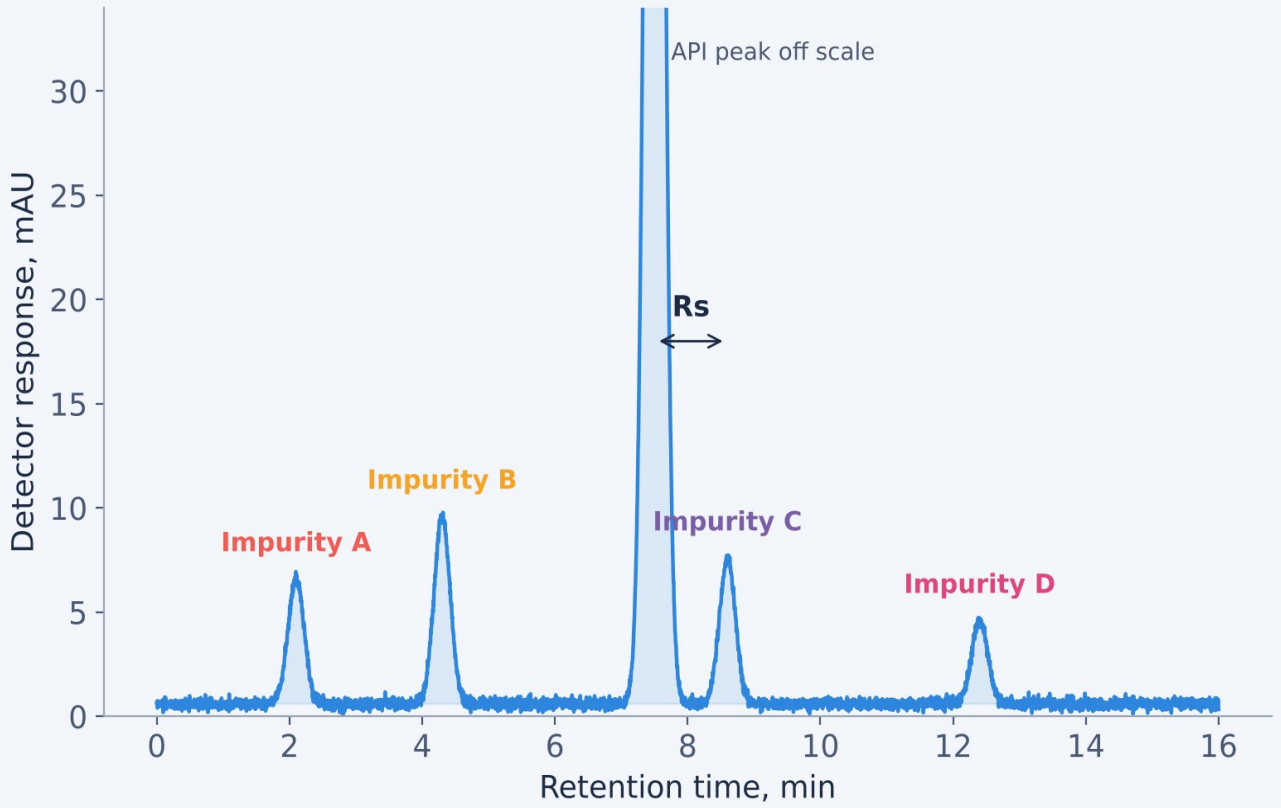
Ash, foreign matter, essential oils, pesticide residues



2.9 Technological tests

Disintegration, dissolution, uniformity, friability, particle size

HPLC: identity, purity and assay in one run



Model chromatogram: API with four related substances

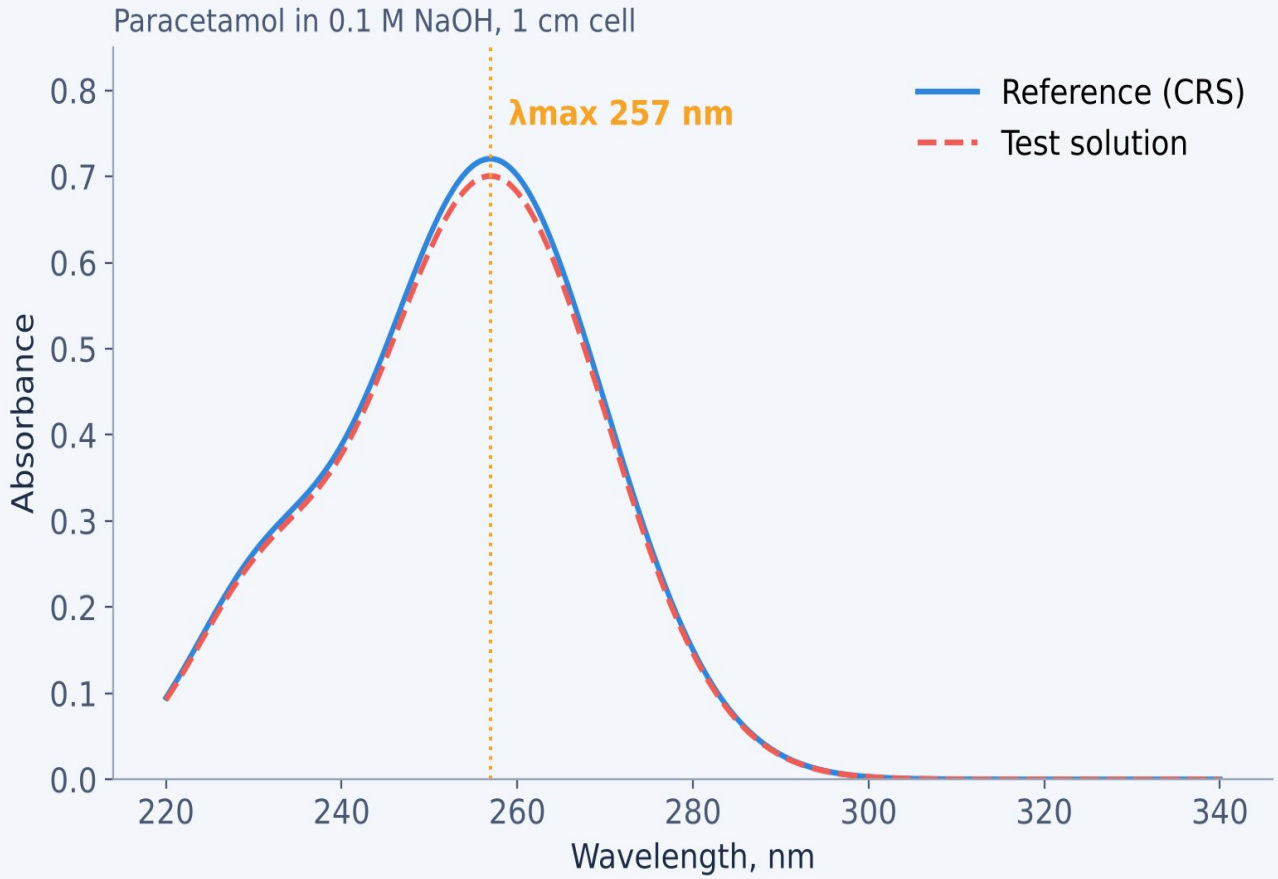
System suitability

- **Resolution:** Rs = 1.18 (tR2 − tR1) / (wh1 + wh2); typically ≥ 1.5
- **Plate number:** N = 5.54 (tR / wh)²
- **Symmetry factor:** As = w0.05 / 2d, 0.8–1.8 unless stated otherwise
- **Repeatability:** RSD of replicate injections within the limit
- **Identity:** tR of test = tR of reference

UV-Vis spectrophotometry and the Beer–Lambert law

Key relations

- **Beer–Lambert:** A = A(1%, 1 cm) · c · l
- **A(1%, 1 cm):** absorbance of a 1 g/100 mL solution in a 1 cm cell
- **Molar absorptivity:** ε = A(1%, 1 cm) · Mr / 10
- **Identity:** λmax and ratio of absorbances
- **Working range:** absorbance about 0.2–0.8 for best precision
- **Checks:** wavelength accuracy, absorbance, stray light, resolution



Titrimetric methods remain the basis of substance assays

Method	Titrant / principle	Example of use
Acid–base (aqueous)	NaOH or HCl; indicator or potentiometry	Acetylsalicylic acid, ascorbic acid, organic acids
Non-aqueous	Perchloric acid in anhydrous acetic acid	Weak bases: alkaloids, amines, many hydrochlorides
Iodometry	Iodine / sodium thiosulfate	Ascorbic acid, metamizole sodium
Nitritometry	Sodium nitrite, diazotisation of aromatic amines	Sulfonamides, procaine, benzocaine
Complexometry	Sodium edetate (EDTA)	Calcium, magnesium, zinc salts
Argentometry	Silver nitrate (Mohr, Volhard, Fajans methods)	Sodium and potassium chloride, bromides
Redox (other)	Potassium permanganate, cerium(IV) sulfate	Hydrogen peroxide, iron(II) salts

Titre

- **T =** c(titrant) × Mr × stoichiometric factor (mg/mL)
- **Content:** m = (V − Vblank) × K × T
- **K** = correction factor of the titrant, 0.95–1.05
- End point: visual indicator or potentiometric

Limit tests and impurity determination

Classical limit tests

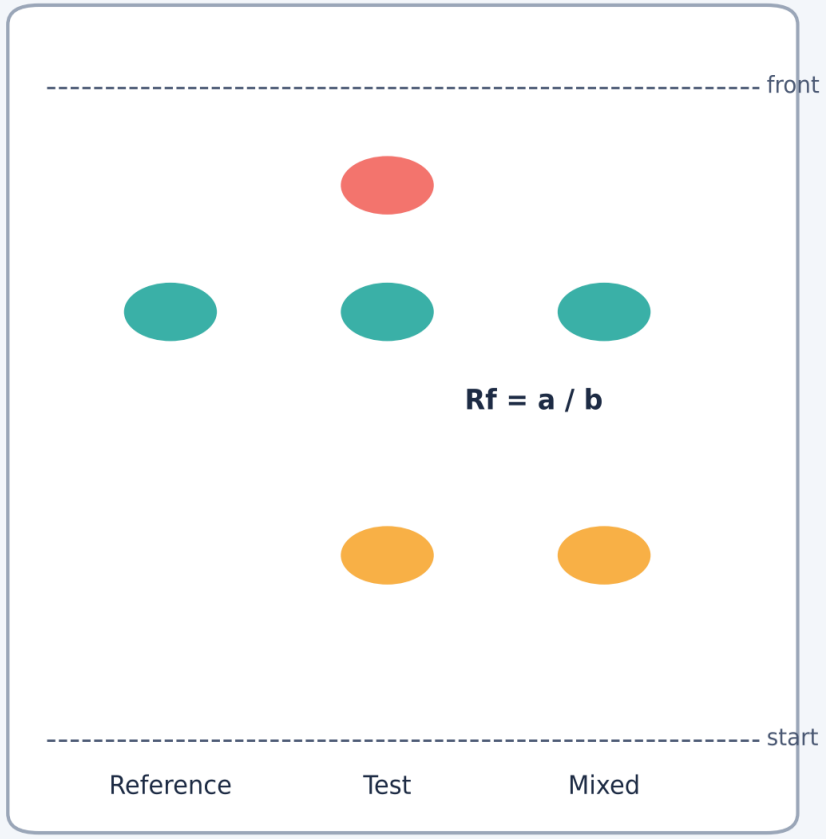
- **Chlorides** 2.4.4, sulfates 2.4.13, iron 2.4.9
- Comparison of opalescence or colour with a standard
- **Loss on drying** 2.2.32; water by Karl Fischer 2.5.12
- **Sulfated ash** 2.4.14: inorganic residue
- Simple, cheap, semi-quantitative

Modern impurity control

- **Related substances** by HPLC or GC, limits per ICH Q3A/Q3B
- **Residual solvents** 2.4.24, ICH Q3C classes 1–3
- **Elemental impurities** 2.4.20, ICH Q3D, ICP-MS or ICP-OES
- **Mutagenic impurities** ICH M7, e.g. nitrosamines
- Quantitative, specific, risk-based

Trend: the classical heavy metals test (2.4.8) has been replaced by risk-based control of elemental impurities (ICH Q3D)

TLC: a simple identity and purity tool



How TLC is used

- **Identity:** the principal spot of the test solution matches the reference in position, colour and size
- **Purity:** any secondary spot is not more intense than the spot of a diluted reference solution
- **Rf** = distance travelled by the spot / distance travelled by the solvent front
- **System suitability:** the chromatogram of the mixed solution shows clearly separated spots
- **Applications:** second identification of substances, herbal drugs, field and pharmacy laboratories

Validation: proving that a method is fit for purpose

Performance characteristic	Identification	Impurities: quantitative	Impurities: limit test	Assay
Specificity / selectivity	+	+	+	+
Accuracy	–	+	–	+
Precision: repeatability	–	+	–	+
Precision: intermediate	–	+	–	+
Range: response (linearity)	–	+	–	+
Detection limit (LOD)	–	–	+	–
Quantitation limit (LOQ)	–	+	–	–



Remember

- + = normally evaluated; – = normally not
- Robustness is studied during development (ICH Q14)
- Pharmacopoeial methods are verified, not fully revalidated, by the user laboratory

QC LABORATORY WORKFLOW

From sample to release decision

1 Sampling

- Representative samples per SOP
- Labelled, sealed, recorded

2 Registration

- Sample log, unique number
- Retained samples kept

3 Testing

- Per specification and SOPs
- Qualified instruments, reference standards

4 Review

- Second-person check of raw data
- ALCOA+ data integrity

OOS?

- Phase I laboratory investigation
- Phase II full investigation

5 Release

- Certificate of analysis
- Batch release by qualified person

Out-of-specification (OOS): a result outside the acceptance criteria is never simply repeated until it passes; it is investigated to find the root cause

Key take-aways

1. **Quality is built in, not tested in:** QA covers the whole system, QC verifies the product
2. **Requirements are written in normative documents:** pharmacopoeias, the normative document on quality, specifications
3. **In Kazakhstan** the Health Code (2020) and EAEU rules (Decisions No. 77, 78, 80) define the framework
4. **Chapter 2 of the Pharmacopoeia** groups the general methods: physicochemical, chemical, biological, technological
5. **Every method must be validated or verified,** and every result must be traceable and reliable

SELF-CHECK

Control questions and literature

Questions

1. Explain the difference between quality assurance and quality control.
2. Which EAEU decisions regulate GMP, registration and GDP?
3. What are the three levels of normative documents? Give an example of each.
4. List the sections of an individual pharmacopoeial monograph.
5. Name the nine groups of general methods in chapter 2 of the Pharmacopoeia.
6. Which system suitability parameters are checked in HPLC?
7. Which validation characteristics are required for an assay and for a limit test?
8. What must a laboratory do when an OOS result is obtained?

Sources

- State Pharmacopoeia of the Republic of Kazakhstan, Vols 1–3
- Pharmacopoeia of the EAEU (EEC Collegium Decision No. 100, 2020)
- European Pharmacopoeia, chapters 2.2–2.9
- Code of the RK No. 360-VI of 07.07.2020
- EEC Council Decisions No. 77, 78, 80 of 03.11.2016
- ICH Q2(R2), Q6A, Q8–Q10, Q14
- WHO TRS 986, Annex 2 (GMP main principles)