LECTURE 3

Quality control of extemporaneous medicines, in-pharmacy stock and perishable preparations



Types of intra-pharmacy control, express analysis and the specific risks of preparations made in the pharmacy

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. Extemporaneous preparations: types and risks
2. System of intra-pharmacy quality control
3. Written, survey, organoleptic and physical control
4. Chemical control and express analysis
5. Refractometry and other quick quantitative methods
6. Purified water, perishable medicines and storage

DEFINITIONS

What the pharmacy prepares



Extemporaneous preparations

Prepared by prescription for an individual patient or by a requirement (order) of a medical organisation



In-pharmacy stock

Small batches of frequently prescribed formulations, prepared in advance and packed



Concentrates and semi-products

Concentrated solutions and triturations used to speed up preparation (burette system)



Why they are needed

Individual doses, children and elderly, absence of industrial forms, hospital needs



Risks

Errors in calculation and weighing, incompatibilities, contamination, short stability



Responsibility

The pharmacist who prepares and the pharmacist-analyst who controls

Key point: an extemporaneous medicine is often used by vulnerable patients, so control must be immediate and complete

Types of intra-pharmacy quality control

1 Preventive	2 Written	3 Survey	4 Organoleptic	5 Physical	6 Chemical	7 At dispensing
• Rules of preparation, storage, sanitary regime • Checking prescription s and doses	Passport of written control (PWC) filled in from memory after preparation	Analyst asks which ingredients and amounts were used	Appearance, colour, odour, homogeneity, absence of visible particles	Total mass or volume, number and mass of doses, closure	Identity (qualitative) and assay (quantitative)	Label, packaging, dose check, patient advice

Mandatory for all preparations: written, organoleptic control and control at dispensing; survey and physical control selectively; chemical control according to the national rules

What can be checked without reagents

Organoleptic control

- **Appearance:** clear or homogeneous, no visible particles
- **Colour** corresponds to the ingredients
- **Odour** characteristic, no foreign odour
- **Homogeneity of powders:** no streaks or spots when pressed
- **Taste:** checked selectively, only for children's medicines, never for toxic substances

Physical control

- **Total mass or volume** compared with the prescription
- **Mass of individual doses** of powders and suppositories
- **Number of doses**
- **Quality of closure,** labelling of the container
- **Deviations** must be within the norms of permissible deviations set by the order

Remember: a clear solution with a wrong colour or an unexpected precipitate is a signal of an error or incompatibility

When full chemical analysis is required

Group of preparations	Scope of chemical control
Solutions for injection and infusion	Before sterilisation: identity and assay of active substances; after sterilisation: pH, identity, assay, isotonising agents
Eye drops and ophthalmic preparations	Identity and assay; sterility and particle requirements for the dosage form
Medicines for newborns and infants	Full analysis (identity and assay)
Concentrates, triturations, semi-products	Full analysis of every batch
In-pharmacy stock	Full analysis of every batch
Other extemporaneous preparations	Qualitative analysis selectively; full analysis of a share of preparations during the shift



Note

- Exact lists and frequencies are set by the order of the MoH RK on intra-pharmacy control
- Results are recorded in the log of chemical control
- Unsatisfactory result → preparation is not dispensed

Drop reactions for rapid identity tests

Chlorides

Silver nitrate in nitric acid: white curdy precipitate, soluble in ammonia

Bromides

Chloramine with hydrochloric acid and chloroform: yellow-brown chloroform layer

Iodides

Iron(III) chloride or sodium nitrite with acid: free iodine, blue with starch

Sodium and potassium

Flame colour: yellow (Na), violet (K, through cobalt glass)

Primary aromatic amines

Diazotisation and coupling with β-naphthol: red-orange azo dye (procaine, sulfonamides)

Phenols, salicylates

Iron(III) chloride: violet colour (sodium salicylate)

Features of express analysis: small volumes (drops), no separation, results in minutes, performed on a spot plate or filter paper

Refractometry: assay in one minute

$n = n0 + C \cdot F$

Basic equation
n_0 = refractive index of water, 1.3330 at 20 °C

$C = (n - n0) / F$

Concentration, %
F = refractive index increment of 1% solution (tables)

20 °C

Temperature control
refractive index depends on temperature and wavelength

- **Example (glucose, F = 0.00142):** n = 1.3472 → C = (1.3472 − 1.3330) / 0.00142 = 10.0%
- **Used for:** concentrates, solutions of one substance, two-component solutions combined with titration

Control of purified water and water for injections

Test	Purified water	Water for injections
Chlorides, sulfates, calcium salts (absence)	Daily, from each container	Each batch
Reducing substances, ammonium, carbon dioxide	Quarterly (full analysis)	Each batch
Full analysis per pharmacopoeia	Quarterly in an accredited laboratory	Quarterly
Microbiological quality	At least twice per quarter	At least twice per quarter, plus endotoxins
Storage	Closed containers, not more than 3 days	Use within 24 hours or sterilise

Why water?

- The most used excipient in the pharmacy
- Chlorides, sulfates, calcium indicate a failure of the still or ion exchanger
- Microbial growth starts quickly in stored water

Why some preparations spoil quickly

Aqueous infusions and decoctions

Rich in nutrients for microbes; stored cool, short shelf life (about 2 days)

Emulsions and suspensions

Physical instability: creaming, sedimentation, microbial growth

Eye drops

Sterile, but contaminated after opening; short use period

Antibiotic solutions

Hydrolysis of β-lactams within hours to days

Cool storage

2–8 °C slows chemical and microbial processes

Protection from light

Coloured glass for photosensitive substances

Aseptic preparation

Clean premises, sterilised equipment, laminar air flow

Labelling

“Keep in a cool place”, “Shake before use”, date of preparation

CASE

Control of an extemporaneous injection solution

1 Prescription	2 Preparation	3 Before sterilisation	4 Sterilisation	5 After sterilisation	6 Dispensing
• Sodium chloride 0.9%, 200 mL for injection • Doses and compatibility checked	• Aseptic unit, WFI, sterile container • PWC filled in	• Identity: chloride, sodium • Assay: argentometry (Mohr), 0.85–0.95%*	• Steam, 120 °C, time by volume • Recorded in the log	• pH, identity, assay, visible particles • Sterility selectively	• Label “For injection”, “Sterile” • Batch, date, expiry



* **Training limit:** compare with the permissible deviations for concentration in the current national order

Key take-aways

1. **Extemporaneous preparations** serve individual and hospital needs but carry specific risks
2. **Intra-pharmacy control** includes preventive, written, survey, organoleptic, physical and chemical control and control at dispensing
3. **Full chemical analysis** is mandatory for injections, eye drops, preparations for infants, concentrates and stock
4. **Express methods and refractometry** give results in minutes
5. **Water and perishable preparations** need strict control, cool storage and short shelf lives

SELF-CHECK

Control questions and literature

Questions

1. Define extemporaneous preparations and in-pharmacy stock.
2. List the types of intra-pharmacy control and say which are mandatory for all preparations.
3. What is the passport of written control and when is it filled in?
4. For which groups is full chemical analysis mandatory?
5. Describe drop reactions for chlorides, bromides and iodides.
6. Calculate the concentration of a glucose solution with n = 1.3401 (F = 0.00142).
7. How often is purified water checked and for which ions?
8. Why do aqueous infusions and eye drops have short shelf lives?

Sources

- Order of the MoH RK on intra-pharmacy quality control (current edition)
- State Pharmacopoeia RK: general monographs on dosage forms; 2.2.6 Refractive index
- Ph. Eur. monographs Purified water (0008), Water for injections (0169)
- Textbooks of pharmaceutical chemistry: express analysis of extemporaneous preparations