LECTURE 4

Quality control of active substances: from synthesis route to impurity profile. Water for pharmaceutical use

How the route of synthesis determines impurities, illustrated by cardiovascular drugs, and how pharmaceutical water is produced and controlled

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. Active substances: sources and quality attributes
2. Impurity classes and ICH thresholds
3. Synthesis routes of cardiovascular drugs and their impurities
4. Nitrosamines: the sartan case
5. Residual solvents and elemental impurities
6. Water for pharmaceutical use

An active substance is more than its formula

Chemical purity

Assay usually 98.0–102.0% or 99.0–101.0%; related substances within limits

Solid-state form

Polymorphs, solvates, amorphous form: affect solubility and stability

Particle size

Critical for dissolution and content uniformity of low-dose tablets

Chirality

Enantiomeric purity: e.g. S-amlodipine, esomeprazole

Water and solvents

Loss on drying or Karl Fischer; residual solvents (ICH Q3C)

Microbial quality

Limits for substances used in non-sterile and sterile products

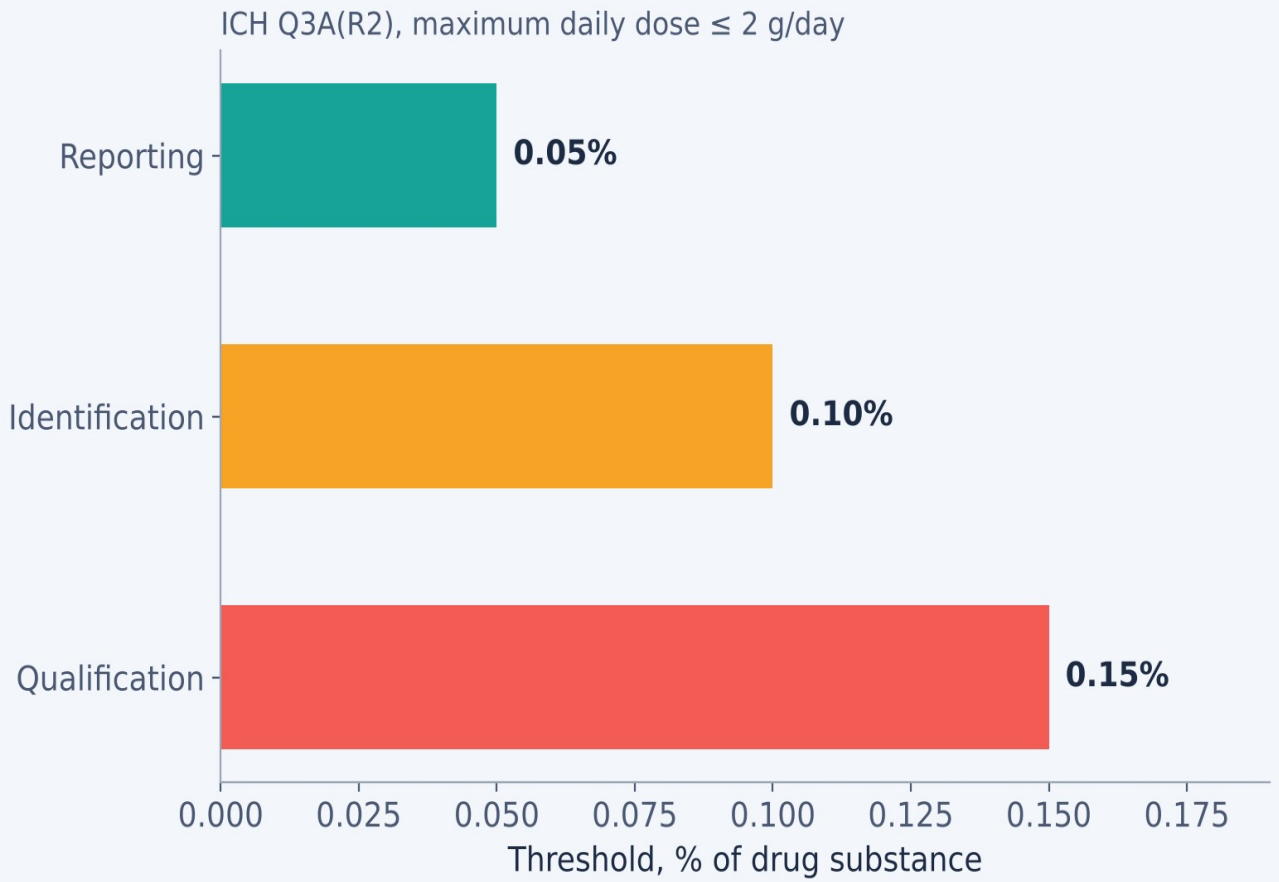
Sources of APIs: chemical synthesis (most cardiovascular drugs), semi-synthesis, fermentation, extraction from plants or animals, biotechnology

Every step of a synthesis can leave a trace

1 Starting materials	2 Intermediates	3 By-products	4 Reagents, catalysts	5 Solvents	6 Degradation
• Impurities of starting materials • Isomers of reagents	• Unreacted intermediates • Over-reaction products	Side reactions, dimers, positional isomers	Pd from coupling reactions, inorganic salts	Residual solvents, solvent-derived impurities	Hydrolysis, oxidation, light during storage

ICH Q3A classifies impurities as: organic (process- and drug-related), inorganic (reagents, catalysts, heavy metals) and residual solvents

Thresholds for impurities in new drug substances



Meaning of the thresholds

- **Reporting:** above 0.05% the impurity is reported in the batch data
- **Identification:** above 0.10% or 1.0 mg/day (whichever is lower) its structure must be identified
- **Qualification:** above 0.15% or 1.0 mg/day its safety must be justified
- **For daily dose > 2 g:** reporting 0.03%, identification and qualification 0.05%
- **Mutagenic impurities:** much lower limits under ICH M7

Cardiovascular drugs: synthesis and critical impurities

Class, example	Key synthetic step	Critical quality issue
Sartans: losartan, valsartan	Biphenyl by Suzuki coupling; tetrazole ring from a nitrile and an azide	Nitrosamines (NDMA, NDEA); residual Pd; azido impurities
β-blockers: metoprolol, atenolol	Phenol + epichlorohydrin → epoxide, then ring opening with isopropylamine	Residual epichlorohydrin (mutagenic); enantiomers
Dihydropyridines: amlodipine	Hantzsch synthesis of the 1,4-dihydropyridine ring	Oxidation to the pyridine derivative (light-sensitive); chirality
ACE inhibitors: enalapril	Reductive amination linking the alanyl-proline fragment	Diketopiperazine (cyclisation); hydrolysis to enalaprilat
Statins: atorvastatin	Paal–Knorr pyrrole synthesis; chiral dihydroxy side chain	Diastereomers; lactone form; oxidation products

The sartan crisis: when a process change created a carcinogen

2018
Valsartan recall
NDMA found in API from a changed synthesis process

96 ng
NDMA acceptable intake per day
EMA / FDA limit

26.5 ng
NDEA acceptable intake per day
EMA / FDA limit

LC-MS
Method of control
and GC-MS: ppb sensitivity

- **Mechanism:** sodium nitrite used to destroy excess azide + secondary amines (e.g. from DMF) → N-nitrosamines
- **Lesson:** every process change needs a risk assessment for mutagenic impurities

Residual solvents and elemental impurities

Residual solvents (ICH Q3C, Ph. Eur. 2.4.24)

- **Class 1, avoid:** benzene 2 ppm, carbon tetrachloride 4 ppm
- **Class 2, limit:** acetonitrile 410 ppm, dichloromethane 600 ppm, toluene 890 ppm, methanol 3000 ppm
- **Class 3, low toxicity:** ethanol, acetone, ≤ 5000 ppm (0.5%) without justification
- **Method:** headspace gas chromatography

Elemental impurities (ICH Q3D, Ph. Eur. 2.4.20)

- **Class 1:** As, Cd, Hg, Pb, toxic in all routes
- **Class 2A:** Co, Ni, V; class 2B: e.g. Pd, Pt (added catalysts)
- **Oral PDE (µg/day):** Cd 5, Pb 5, As 15, Hg 30
- **Method:** risk assessment; ICP-MS or ICP-OES

Grades of water and their limits (Ph. Eur.)

Parameter	Purified water (bulk)	Water for injections (bulk)
Production	Distillation, ion exchange, reverse osmosis or other suitable method	Distillation, or reverse osmosis plus other techniques equivalent to it
Conductivity	≤ 5.1 µS/cm at 25 °C	≤ 1.3 µS/cm at 25 °C (stage 1)
Total organic carbon	≤ 0.5 mg/L (or oxidisable substances)	≤ 0.5 mg/L
Nitrates	≤ 0.2 ppm	≤ 0.2 ppm
Microbial count	≤ 100 CFU/mL (action level)	≤ 10 CFU/100 mL (action level)
Bacterial endotoxins	—	< 0.25 IU/mL
Typical use	Oral and topical preparations, rinsing	Parenteral preparations, final rinse of sterile equipment

A typical purified water and WFI system

1 Pre-treatment	2 Reverse osmosis	3 EDI	4 Distillation / UF	5 Storage and loop	6 Monitoring
• Sand and carbon filters (chlorine removal) • Softening	• Removes ions, organics, microbes • Often double-pass	Electrodeionisation polishes conductivity	Multi-effect still or ultrafiltration for WFI	• Continuous circulation • Hot loop ≥ 65 °C or ozone / UV	• On-line conductivity and TOC • Microbial sampling at points of use

Validation: three phases over about one year cover seasonal changes in feed water; biofilm is the main enemy of any water system

Key take-aways

1. **API quality includes** purity, solid-state form, particle size, chirality, solvents and microbial quality
2. **ICH Q3A thresholds** (0.05 / 0.10 / 0.15%) decide reporting, identification and qualification
3. **The synthesis route** determines the impurity profile, as cardiovascular drugs show
4. **Nitrosamines and other mutagenic impurities** are controlled at ng/day levels (ICH M7)
5. **Water for injections** needs conductivity ≤ 1.3 µS/cm, endotoxins < 0.25 IU/mL and a well-designed loop

SELF-CHECK

Control questions and literature

Questions

1. Which quality attributes of an active substance besides assay are important and why?
2. State the ICH Q3A thresholds for a daily dose ≤ 2 g.
3. Name the sources of impurities in a synthesis.
4. Explain how NDMA was formed in valsartan.
5. Give examples of class 1, 2 and 3 residual solvents with limits.
6. Which elements belong to class 1 of ICH Q3D?
7. Compare the limits for purified water and water for injections.
8. Why is a water loop kept hot or sanitised?

Sources

- Ph. Eur. 2034 Substances for pharmaceutical use; 0008 Purified water; 0169 Water for injections
- ICH Q3A(R2), Q3C, Q3D(R2), M7(R2)
- EMA: Nitrosamine impurities in human medicinal products (Art. 5(3) review, 2020)
- State Pharmacopoeia RK, Vols 1–3