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B.PHARM SEMESTER I

Pharmaceutical Inorganic and Analytical Chemistry

(Course Code: BP106T)

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UNIT I

Pharmaceutical Analysis, Errors and Impurities

SHORT NOTES

Condensed Study Notes for Quick Revision (PCI Syllabus, NEP 2020)

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Short notes for Unit I, covering pharmaceutical analysis, errors, and impurities. Written as condensed bullets and quick-reference tables rather than full prose, for fast revision after the detailed unit has already been studied.

1.1 Introduction to Pharmaceutical Analysis

Introduction to Pharmaceutical Analysis

Pharmaceutical analysis is the branch of pharmaceutical science concerned with the **identification, separation, qualitative and quantitative determination, and purity testing of drugs and pharmaceutical substances**.

It is essential for ensuring that medicines are **safe, effective, pure, and of consistent quality**.

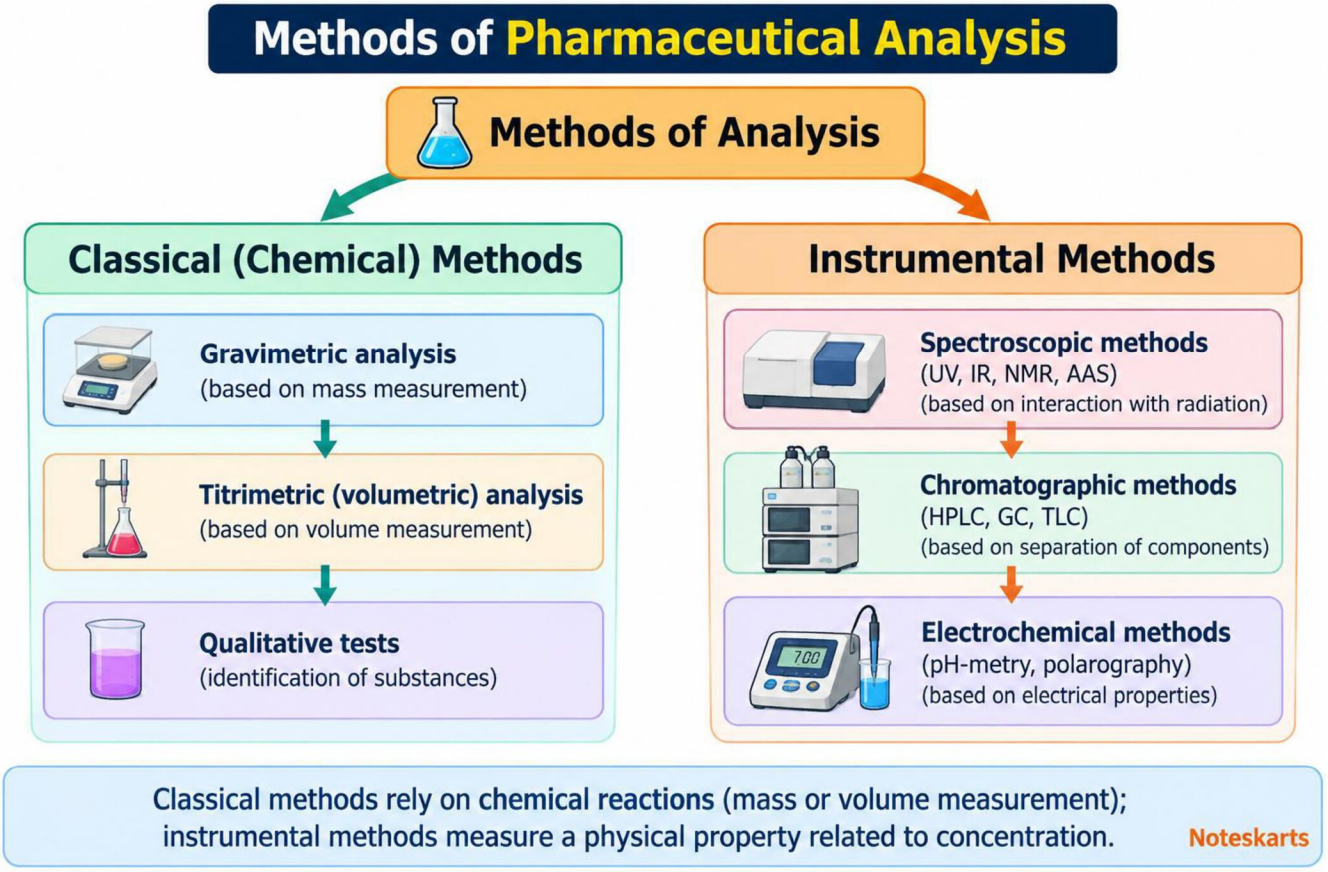
Importance of Pharmaceutical Analysis

- Helps to **identify** drug substances and excipients.
- Determines the **amount or concentration** of active pharmaceutical ingredients (APIs).
- Detects **impurities and contaminants**.
- Ensures the **purity and quality** of pharmaceutical products.
- Helps confirm the **strength and potency** of medicines.
- Ensures that products comply with **official pharmacopoeial standards**.
- Supports **quality control (QC)** and **quality assurance (QA)** during pharmaceutical manufacturing.

Main Types

1. **Qualitative Analysis** – identifies **what substances are present**.
2. **Quantitative Analysis** – determines **how much of a substance is present**.

- Quality Control (QC): testing/inspection of the finished product against specifications — a reactive, end-point check.
- Quality Assurance (QA): the broader system that builds quality into every step of production — proactive, covers documentation, training, process design.
- Pharmacopoeial standards (IP, BP, USP) define identity, purity, strength, and quality tests every official drug substance must pass.



Classification of methods of analysis

Feature	Classical (Wet Chemical)	Instrumental
Basis	Stoichiometric reaction, weight/volume	Physical property proportional to concentration
Examples	Gravimetry, titrimetry	Spectroscopy, chromatography, electrochemical
Sensitivity	Lower (mg–g range)	Higher (trace/ppm levels)
Speed	Slower, manual	Faster, often automated
Equipment cost	Low	Higher

- Gravimetry: analyte converted to a pure, insoluble, weighable compound of known composition.
- Titrimetry (volumetric analysis): volume of a standard reagent required to react completely with the analyte is measured.

Concentration Expressions

Unit	Meaning
% w/v	g of solute per 100 mL of solution
% w/w	g of solute per 100 g of solution
% v/v	mL of solute per 100 mL of solution
Molarity (M)	moles of solute per litre of solution

Unit	Meaning
Normality (N)	gram-equivalents of solute per litre of solution
Molality (m)	moles of solute per kg of solvent
ppm / ppb	parts per million / billion

WORKED EXAMPLE — % W/V TO MOLARITY

A solution is 4.9% w/v H_2SO_4 (mol. wt. 98). Find its molarity.

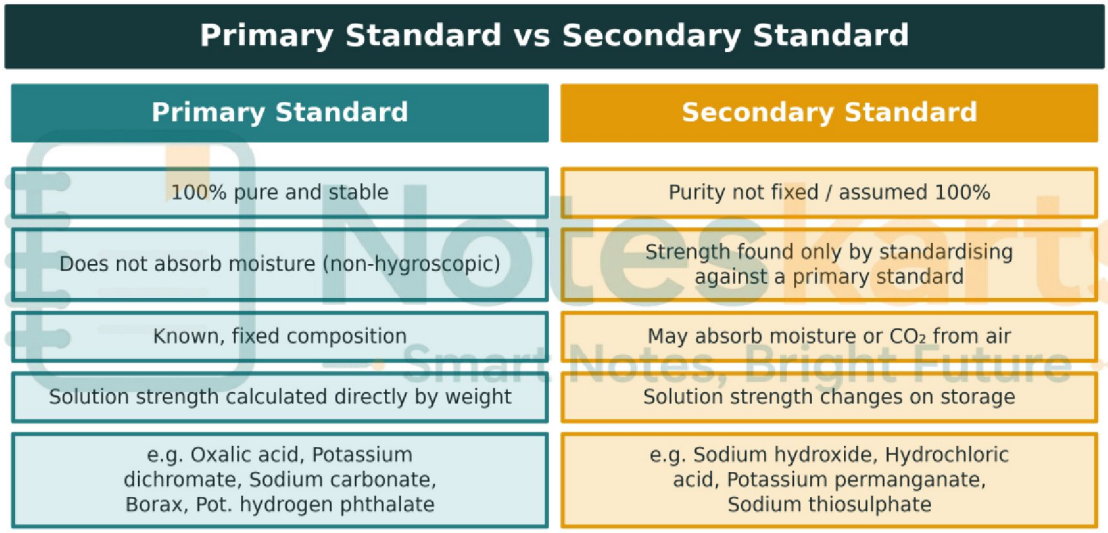
Grams per litre = 4.9 × 10 = 49 g/L; Molarity = 49/98 = 0.5 M

WORKED EXAMPLE — NORMALITY

3.15 g of oxalic acid ($H_2C_2O_4 \cdot 2H_2O$, mol. wt. 126, eq. wt. 63) in 250 mL.

Equivalents = 3.15/63 = 0.05 eq; Normality = 0.05/0.25 = 0.20 N

Primary and Secondary Standards



Primary vs secondary standards

- Primary standard requirements: high purity (>99.9%), stable in air, non-hygroscopic, high equivalent weight, reacts in a single known way.

Primary Standard	Used to Standardise
Anhydrous Na_2CO_3 / Borax	Acids (HCl, H_2SO_4)
Potassium hydrogen phthalate (KHP)	Bases (NaOH)
Oxalic acid	Bases; $KMnO_4$
Potassium dichromate / Potassium iodate	Sodium thiosulphate
Sodium chloride	$AgNO_3$
Calcium carbonate	EDTA

- Secondary standard: strength not known from purity alone — must be standardised against a primary standard. E.g. HCl, NaOH, $KMnO_4$, $Na_2S_2O_3$, $AgNO_3$, EDTA.

- Equivalent weight = molecular weight ÷ n (n = replaceable H^+/OH^-, electrons transferred, or ionic charge, depending on reaction type).

WORKED EXAMPLE — MOLARITY TO NORMALITY

Convert 0.5 M H_2SO_4 to Normality. Since H_2SO_4 has 2 replaceable H^+ (n=2):

Normality = Molarity × n = 0.5 × 2 = 1.0 N

- **Molarity and Normality**
  - Molarity (M) and Normality (N) are equal when the **n-value = 1**.
  - Examples: **HCl, NaOH**
  - When **n = 2 or 3**:
    - **Normality = n × Molarity**
  - Examples:
    - H_2SO_4, Na_2CO_3 → **N = 2M**
    - For an n = 3 substance → **N = 3M**

- **Direct Weighing**
  - The sample is **weighed directly** on the analytical balance.
  - The displayed weight is taken as the sample weight.

- **Weighing by Difference**
  - The **container + sample** are weighed first.
  - After transferring the sample, the **container is weighed again**.
  - The difference between the two weights gives the **actual sample weight**.
  - This method helps minimise **tare/zero-point errors** and provides greater accuracy.

- **Preparation of Standard Solutions**
  - Standard solutions are prepared accurately using **volumetric flasks**.
  - A **calibrated analytical balance** should be used for accurately weighing primary standards.
  - **Top-loading balances should not be used** when the required accuracy calls for an analytical balance.

WORKED EXAMPLE — PREPARING A STANDARD SOLUTION

Prepare 500 mL of 0.1 N Na_2CO_3 (eq. wt. 53). What weight is needed?

Equivalents needed = 0.1 × 0.500 = 0.05 eq; Weight = 0.05 × 53 = 2.65 g

Dissolve 2.65 g in water and make up to exactly 500 mL in a volumetric flask.

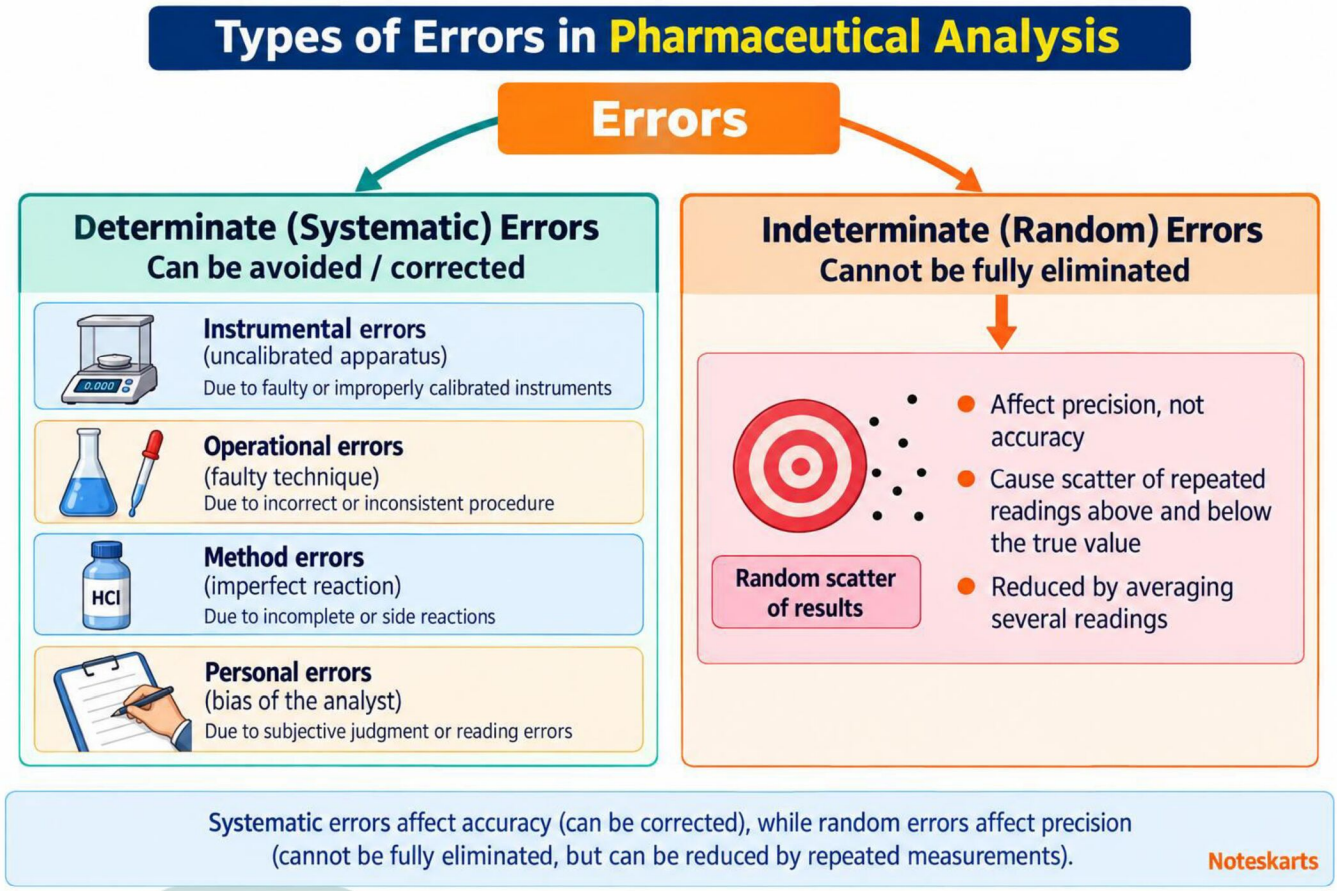
- Dilution formula: $C_1V_1 = C_2V_2$, used to prepare a weaker solution from a stronger stock solution.

WORKED EXAMPLE — DILUTION

How much of a 2 M stock solution is needed to prepare 250 mL of 0.5 M solution?

$C_1V_1 = C_2V_2$ → 2 × V_1 = 0.5 × 250 → V_1 = 62.5 mL, made up to 250 mL with solvent.

1.2 Errors in Pharmaceutical Analysis



Classification of errors in quantitative analysis

Error Type	Nature	Example
Determinate (systematic)	Definite cause, one-directional, correctable	Instrumental, operational, method, personal errors
Indeterminate (random)	No fixed cause, both directions, normal distribution	Reading fluctuations, minor unavoidable variations

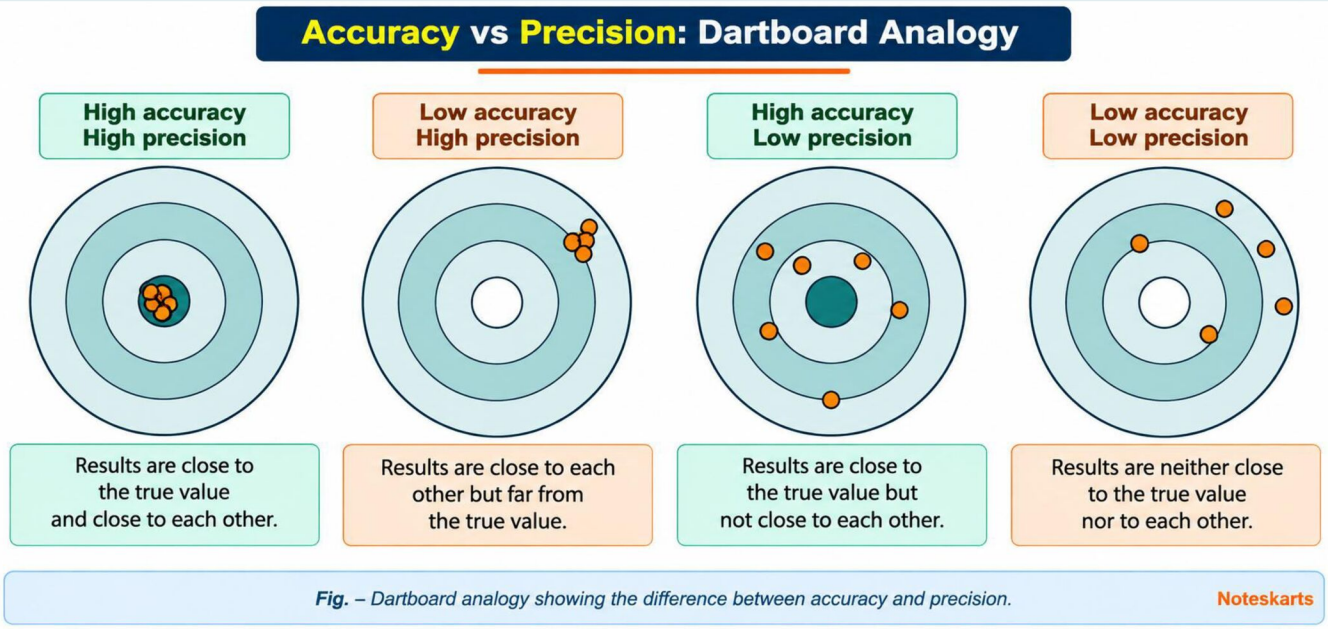
▸ Four Subtypes of Determinate Error

- Instrumental: faulty/uncalibrated equipment (balance, pipette, pH meter).
- Operational: technique mistakes (incomplete precipitation, sample loss, overheating).
- Method (additive/proportional): built into the method's own chemistry (co-precipitation, indicator error).
- Personal: observer bias (meniscus reading habit, colour perception).

Error Subtype	Behaviour
Additive error	Constant value, independent of sample size
Proportional error	Increases in direct proportion to sample size

- Minimising errors: calibrated equipment, blank determinations, control samples, replicate titrations, standard addition method.

Accuracy and Precision



Accuracy vs precision — dartboard analogy

- Accuracy: closeness of a result (or mean of results) to the true/accepted value.
- Precision: closeness among repeated measurements, regardless of closeness to the true value.
- A result can be precise but not accurate (systematic bias) or accurate on average but not precise (random scatter).
- Repeatability: precision when the same analyst repeats the test, same day, same equipment.
- Reproducibility: precision when the test is repeated by different analysts/days/labs.

KEY FORMULAS

% Error = [(Observed − True)/True] × 100

Mean deviation = Σ|xi − mean| / n

Standard deviation (s) = √[Σ(xi − mean)² / (n−1)]

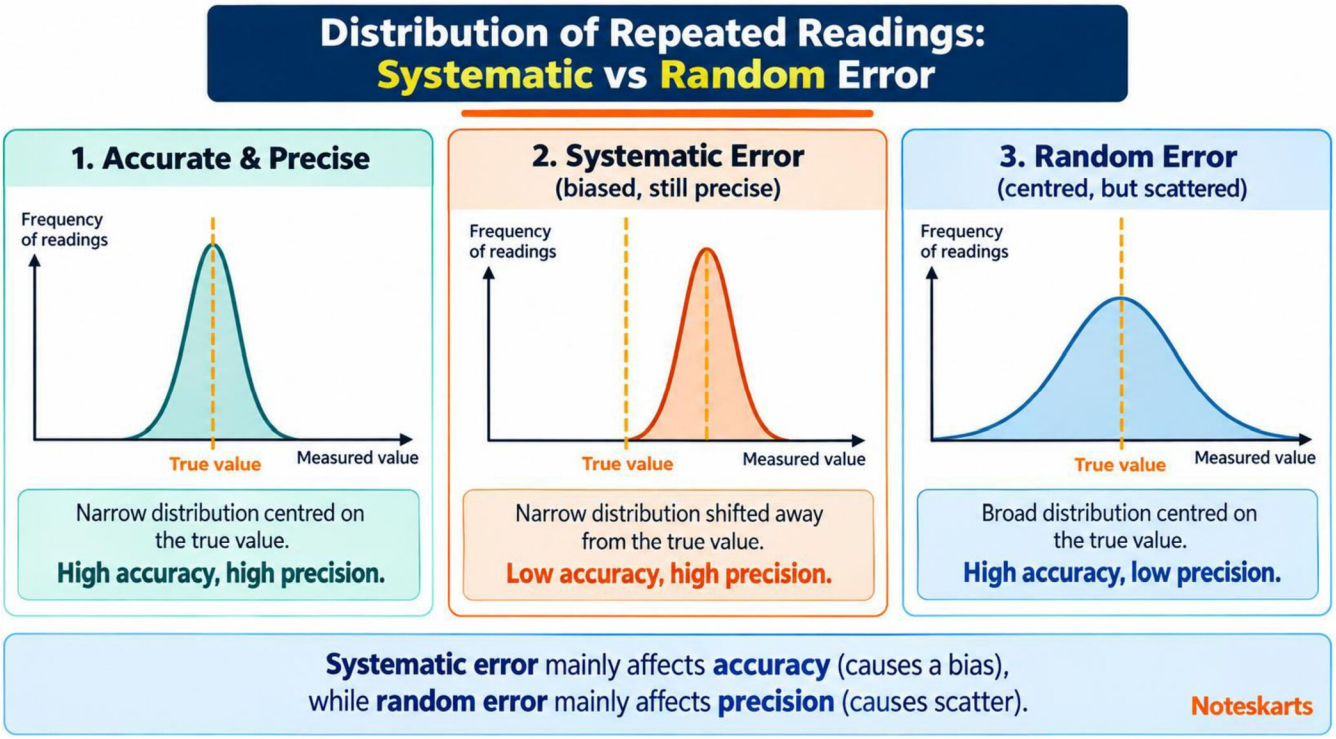
Relative standard deviation (RSD %) = (s/mean) × 100

WORKED EXAMPLE — STANDARD DEVIATION

Titration values (mL): 24.9, 25.1, 25.0, 24.8, 25.2. Mean = 25.0

Deviations²: 0.01, 0.01, 0, 0.04, 0.04; Σ = 0.10

s = √(0.10/4) = 0.158 — small SD indicates good precision.



Systematic vs random error distributions

Significant Figures

- A significant figure is any digit known with certainty, plus one final estimated digit.
- Rules: non-zero digits always significant; zeros between non-zero digits significant; leading zeros not significant; trailing zeros after a decimal point significant.
- Addition/subtraction: answer has as many decimal places as the term with fewest. Multiplication/division: answer has as many sig figs as the term with fewest.
- Keep guard digits through intermediate steps; round only the final answer.

WORKED EXAMPLE — SIGNIFICANT FIGURES IN CALCULATION

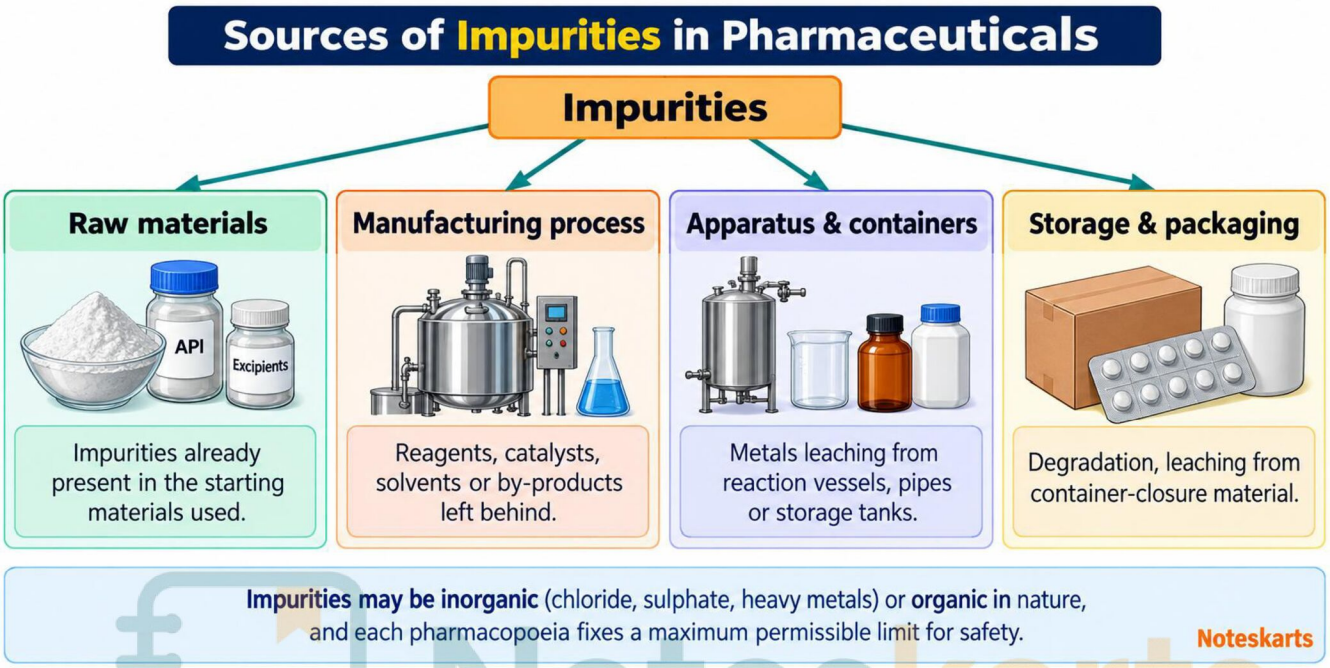
Add 12.11 + 18.0 + 1.013. The term with fewest decimal places is 18.0 (1 decimal place).

Raw sum = 31.123; rounded to 1 decimal place = 31.1

- Rounding rule: if the digit dropped is exactly 5 with nothing after it, round to the nearest even digit (banker's rounding), used in some pharmacopoeial contexts to avoid systematic upward bias.
- Coefficient of variation (CV%) = RSD% = (s/mean) × 100 — allows comparing precision between methods/instruments with very different absolute magnitudes.
- Confidence limits: the true value is expected to lie within mean ± (t × s/√n) at a chosen confidence level (commonly 95%), where t is the Student's t-value for (n−1) degrees of freedom.
- Q-test (outlier test): used to decide whether a suspect result, much higher or lower than the rest, should be rejected before calculating the mean/SD, based on a critical Q-value for the given number of readings.

- Gross error: a major blunder (e.g. using the wrong reagent, a large calculation mistake) that invalidates a result entirely — distinct from ordinary determinate or indeterminate error, and the result is normally discarded and the analysis repeated.

1.3 Impurities in Pharmaceuticals



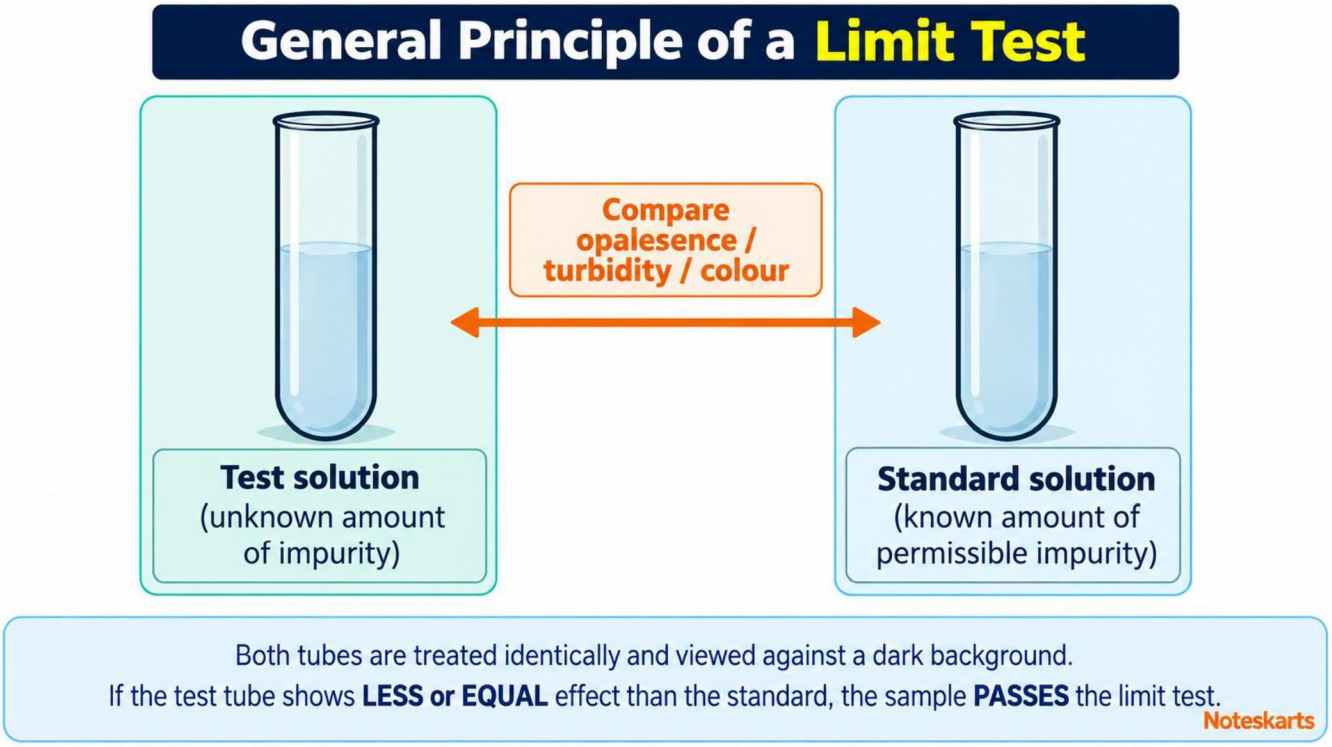
Sources of impurities in pharmaceutical substances

- **Sources:** raw materials, reagents/solvents in synthesis, the manufacturing process itself, storage/packaging (leaching, degradation), natural shelf-life degradation.

ICH Guideline	Covers
Q3A	Impurities in new drug substances
Q3B	Impurities in new drug products
Q3C	Residual solvents
Q3D	Elemental impurities (metals)

- Impurities are controlled by a specified limit in the monograph, not necessarily eliminated entirely.

Principle of a Limit Test



General principle of a limit test (Nesslerization)

- A **limit test** is a simple test used to check whether a small amount of a particular **impurity** is within the permitted limit.
- It is a **semi-quantitative test**, meaning it does not give the exact amount of impurity.
- The **sample and standard solution** are treated in exactly the same way.
- The standard contains the **maximum permitted amount of the impurity**.
- The colour or turbidity produced in the sample is compared with the standard.

Nesslerization

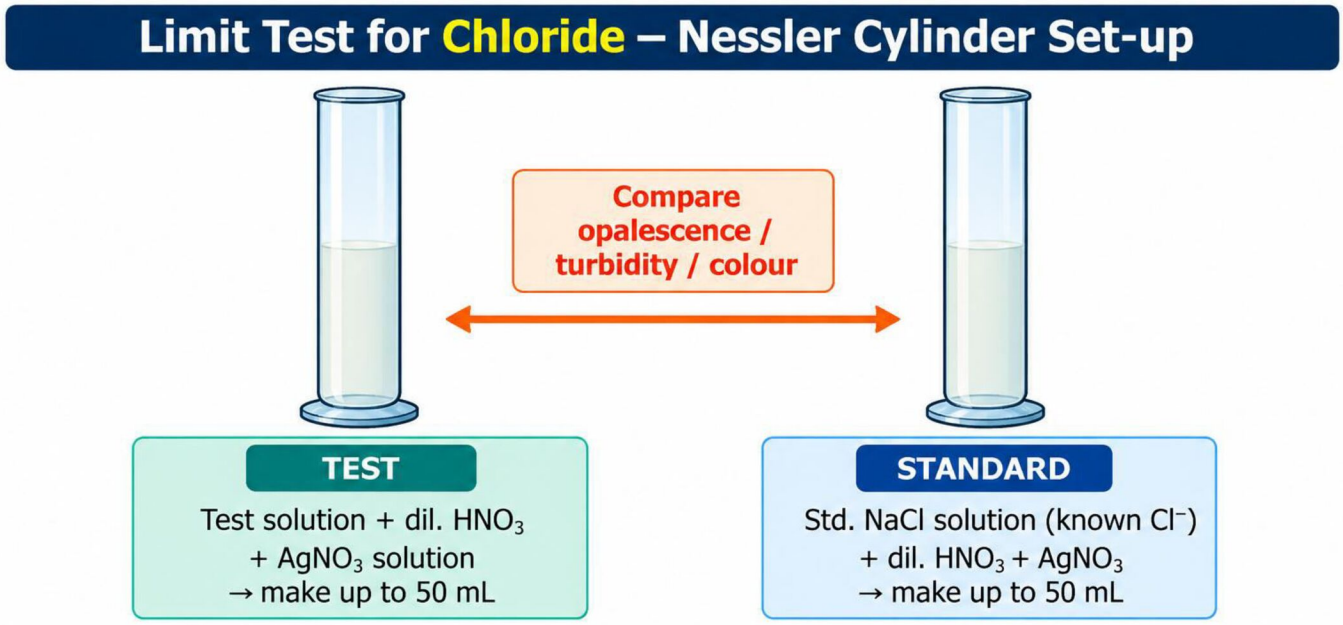
- Nesslerization is a common method used in some limit tests.
- The **sample and standard** are placed in matched **Nessler cylinders**.
- They are compared by looking **downward through the solutions** against a **white background**.
- If the sample is **not more intense** in colour or turbidity than the standard, it passes the test.

General Precautions

- Use **pure, impurity-free water and reagents**.
- Add reagents to both the **sample and standard in the same order**.
- Keep the **reaction time the same** for both.
- Allow both solutions to stand for the **same amount of time** before comparison.
- Use **clean and properly matched Nessler cylinders**.

Individual Limit Tests

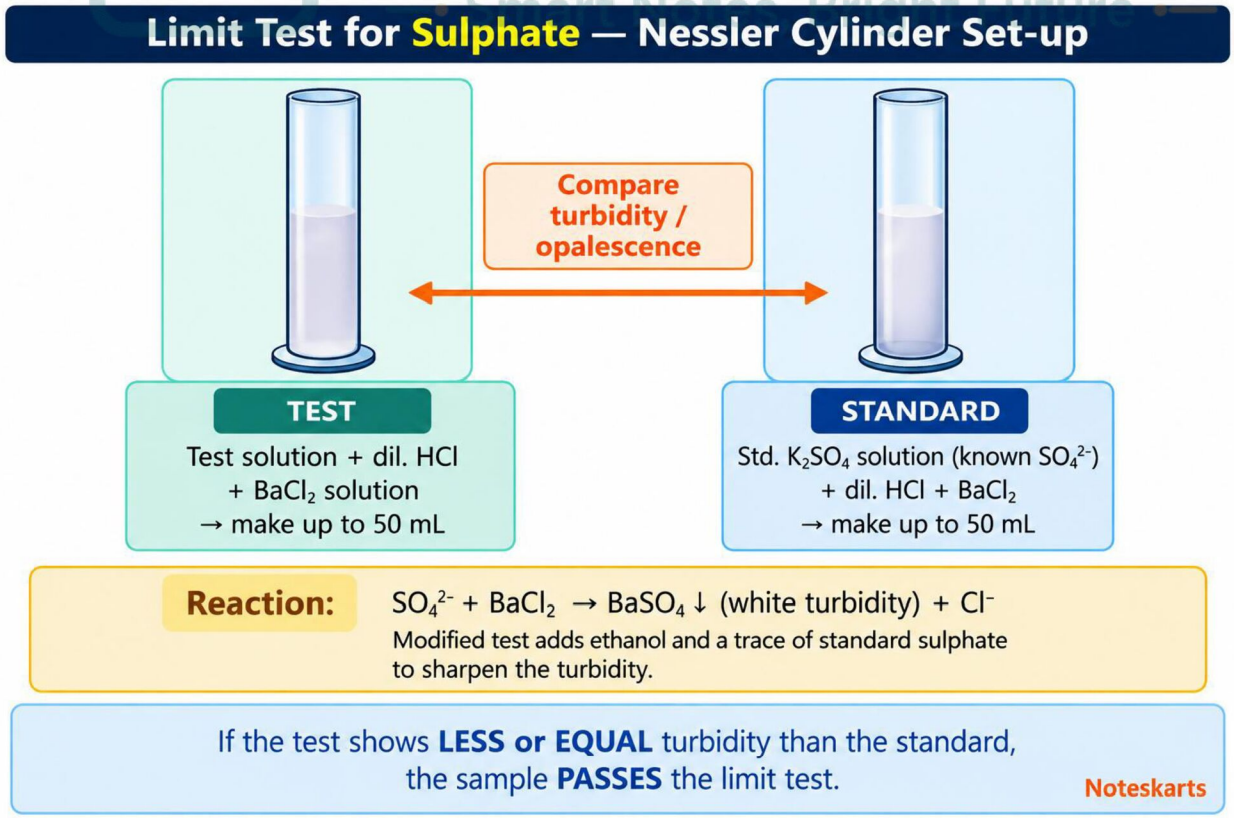
▸ Chloride



Limit test for chloride

- $Cl^- + AgNO_3 \rightarrow AgCl\downarrow$ (white turbidity), in dilute HNO_3 medium.

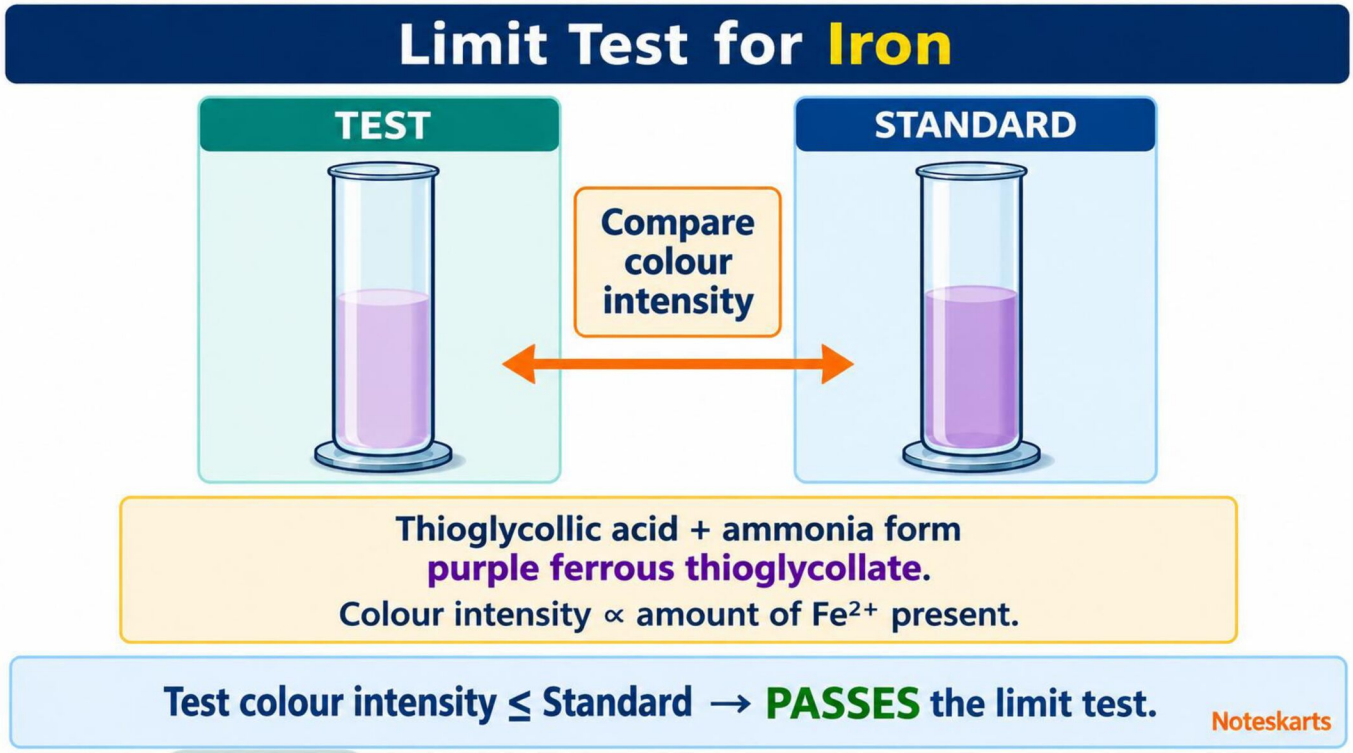
▸ Sulphate



Limit test for sulphate

- $SO_4^{2-} + BaCl_2 \rightarrow BaSO_4\downarrow$ (white turbidity), in dilute HCl medium.

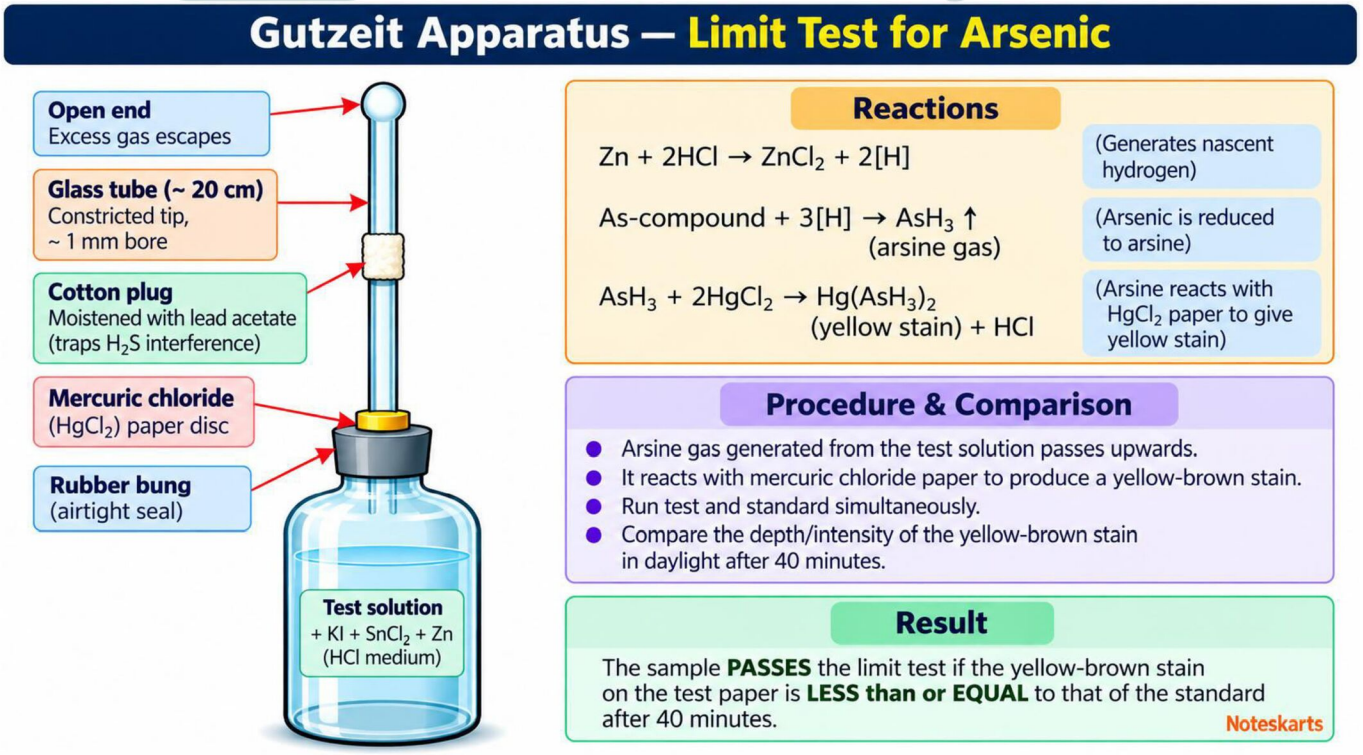
▸ Iron



Limit test for iron

- Fe^{3+} + thioglycollic acid, ammoniacal solution → purple/pink colour, compared with a standard iron solution.

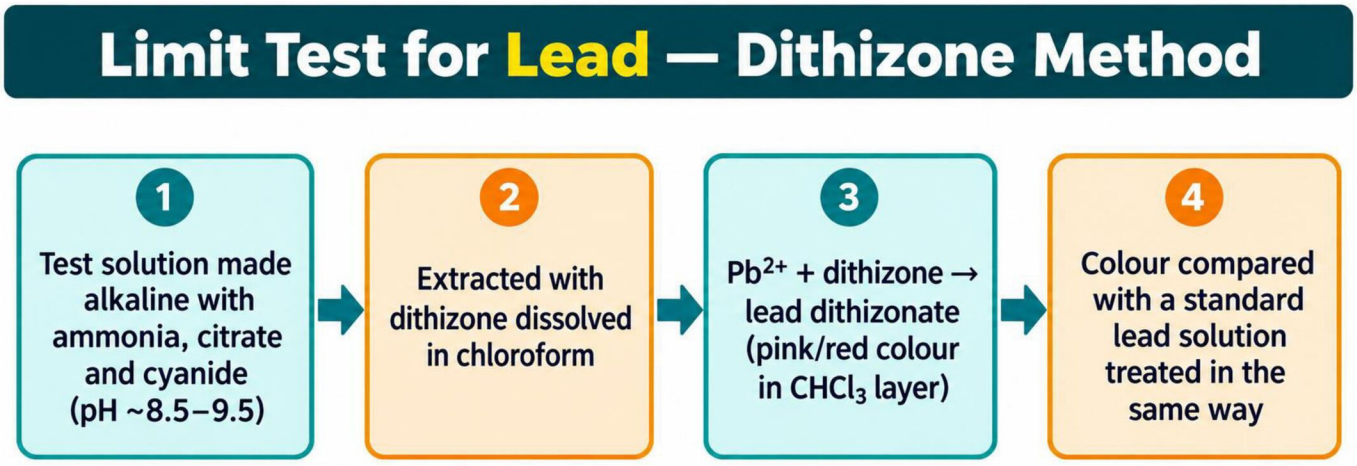
▸ Arsenic (Gutzeit Method)



Gutzeit apparatus for the arsenic limit test

- Sample + zinc + acid generates arsine gas (AsH_3), staining mercuric chloride paper yellow-to-brown; stain compared with a standard.
- Precautions: arsenic-free zinc/reagents, apparatus checked for leaks, identical generation time for sample and standard.

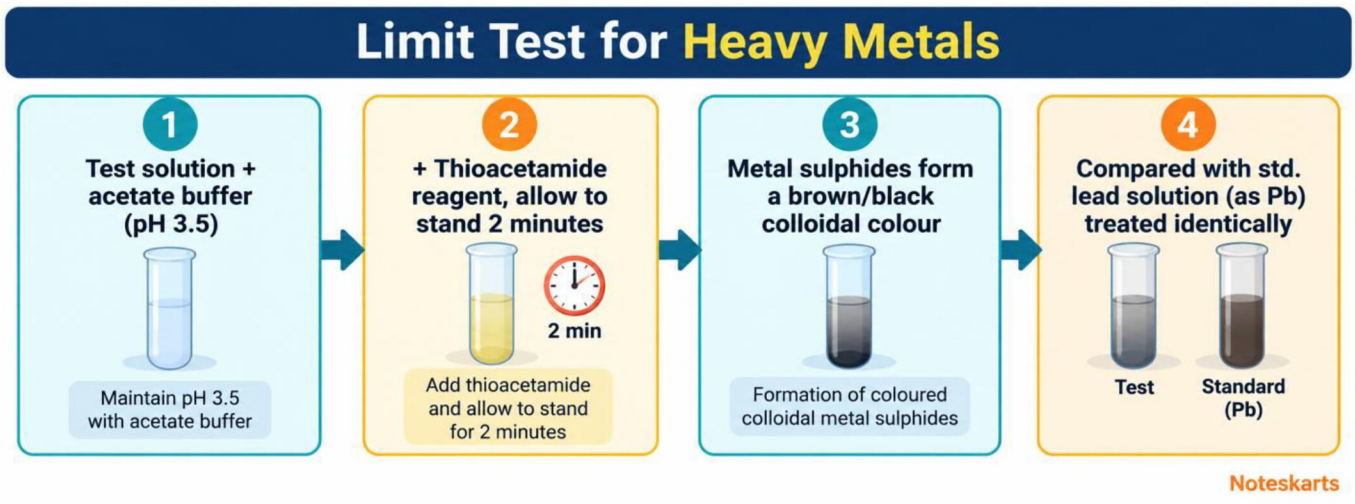
▸ Lead



Limit test for lead (dithizone method)

- Pb^{2+} extracted into chloroform as lead dithizonate (pink/red), at controlled pH 8.5–10 (ammonia-cyanide buffer); compared with a standard.
- Precautions: strict pH control, redistilled/lead-free solvents and glassware.

▸ Heavy Metals (General)



Limit test for heavy metals

- Sample + thioacetamide reagent, acetate buffer pH 3.5 → brown colour (metal sulphides), compared with a lead standard.

▸ Summary Table — Limit Tests

Test	Key Reagent	Colour/Turbidity
Chloride	$AgNO_3$	White turbidity
Sulphate	$BaCl_2$	White turbidity
Iron	Thioglycollic acid	Purple/pink
Arsenic	Zinc + acid; $HgCl_2$ paper	Yellow-brown stain
Lead	Dithizone, $CHCl_3$, pH 8.5–10	Pink/red in $CHCl_3$ layer
Heavy metals	Thioacetamide, pH 3.5	Brown colour

COMMON MISTAKE

Comparing sample and standard side-by-side but prepared at different times, or with reagents added in a different order, invalidates a limit test — both must be treated identically, since even small timing/order differences change the turbidity or colour intensity observed.

- Nessler cylinders must be of matched, identical diameter — comparing turbidity in cylinders of different width is a common practical error, since turbidity is judged by looking down through the depth of liquid.
- Limit tests are semi-quantitative (pass/fail against a defined maximum), unlike a full quantitative assay which gives an exact numerical result.
- Arsenic limit test precaution: the test must be run for exactly the same generation time for sample and standard, since AsH_3 generation and staining intensity both depend on reaction time, not just arsenic content.
- Lead limit test precaution: glassware is rinsed with dilute nitric acid before use, since ordinary glass can itself leach trace lead, giving a falsely high blank reading.
- Heavy metals test: thioacetamide slowly hydrolyses in the acetate buffer to release H_2S, which precipitates metal sulphides — freshly prepared reagent is important, since aged thioacetamide reagent gives weaker, less reliable colour development.

▸ Key Terms — Unit I

Term	Meaning
Accuracy	Closeness of a result to the true value
Precision	Closeness among repeated measurements
Primary standard	Substance of known purity used to standardise a titrant directly
Limit test	Semi-quantitative comparison of sample vs standard for a specified impurity
Nesslerization	Comparing colour/turbidity in matched cylinders under identical conditions