CHALLENGES IN ICP-MS ANALYSIS OF ELEMENTAL IMPURITIES IN PHARMACEUTICAL PRODUCTS

METHODOLOGICAL AND ANALYTICAL CONSIDERATIONS

Biljana Balabanova, Full Professor,
Faculty of Agriculture, Goce Delcev University, Krste Misirkov bb, 2000 Stip, Republic of North Macedonia
biljana.balabanova@ugd.edu.mk
www.ugd.edu.mk
www.unilab.ugd.edu.mk

ICNTC CONFERENCE
INTERNATIONAL CONFERENCE ON NEW TRENDS IN CHEMISTRY

25th – 27th of April, 2025, Bologna Italy

ELEMENTAL IMPURITIES IN PHARMACEUTICAL PRODUCTS

- Elemental impurities in pharmaceutical products refer to **trace levels of metals and metalloids** that can be present in drug substances, excipients, or final drug products.
- These impurities can originate from raw materials, manufacturing equipment, processing aids, or packaging systems and can pose **toxicological risks** to patients if not properly controlled.

ELEMENTAL IMPURITIES IN PHARMACEUTICAL PRODUCTS

- The analysis of elemental impurities in pharmaceutical products using Inductively Coupled Plasma with Mass Spectrometry (ICP-MS) is critical for ensuring product safety and efficacy.
- This approach, guided by regulatory frameworks like USP <232>/<233> and ICH Q3D, addresses several challenges and considerations:

WHY ARE ELEMENTAL IMPURITIES IMPORTANT?

- Toxicity: Even in trace amounts, some elements (like arsenic, lead, cadmium, and mercury) are highly toxic and can cause organ damage, cancer, or developmental issues.
- Regulatory Compliance: Regulatory bodies like the ICH and USP have developed strict guidelines (ICH Q3D, USP <232> and <233>) to limit permissible levels of these impurities.
- Product Safety and Quality: Ensuring low levels of elemental impurities is critical for the efficacy and safety of pharmaceutical products.

WHY ARE ELEMENTAL IMPURITIES IMPORTANT?

- The ICH (International Council for Harmonisation) Q3 guidelines provide a framework for managing impurities in drug substances and products.
- Specifically, ICH Q3A focuses on impurities in new drug substances, Q3B addresses impurities in new drug products, and Q3C deals with residual solvents.

WHY ARE ELEMENTAL IMPURITIES IMPORTANT?

- The ICH (International Council for Harmonisation) Q3 guidelines provide a framework for managing impurities in drug substances and products.
- Specifically, ICH Q3A focuses on impurities in new drug substances, Q3B addresses impurities in new drug products, and Q3C deals with residual solvents.
- Chapter 232 ELEMENTAL IMPURITIES—LIMITS (The United States Pharmacopeia)

REGULATORY FRAMEWORKS

ICH Q3D (International Council for Harmonisation)

Class	Included elemental impurity
Class 1	Arsenic, Lead, Cadmium, Mercury
Class 2A	Cobalt, Vanadium, Nickel
Class 2B	Thallium, Gold, Palladium, Iridium, Osmium, Rhodium, Ruthenium, Selenium, Silver, Platinum
Class 3	Lithium, Antimony, Barium, Molybdenum, Copper, Tin, Chromium

- The method used for establishing the PDE for each elemental impurity is discussed in "Q3D (R1) Guideline for elemental impurities" in detail.
- Elements evaluated in this guideline were assessed by reviewing the publicly available data contained in scientific journals, government research reports and studies, international regulatory standards (applicable to drug products) and guidance, and regulatory authority research and assessment reports.

REGULATORY FRAMEWORKS

		Oral (µg/day)	Parenteral (µg/day)	Inhalation (µg/day)	Final dose form dietary supplements
Class 1	Cd - Cadmium	5	2	2	5
	Pb - Lead	5	5	5	10
	As - Arsenic	15	15	2	15
	Hg - Mercury	30	3	1	15
Class 2A	Co - Cobalt	50	5	3	
	V - Vanadium	100	10	1	
	Ni - Nickel	200	20	5	
Class 2B	Tl - Thallium	8	8	8	
	Au - Gold	100	100	1	
	Pd - Palladium	100	10	1	
	Ir - Iridium	100	10	1	
	Os - Osmium	100	10	1	
	Rh - Rhodium	100	10	1	
	Ru - Ruthenium	100	10	1	
	Se - Selenium	150	80	130	
	Ag - Silver	150	10	7	
	Pt - Platinum	100	10	1	
Class 3	Li - Lithium	550	250	25	
	Sb - Antimony	1200	90	20	
	Ba - Barium	1400	700	300	
	Mo - Molybdenum	3000	1500	10	
	Cu - Copper	3000	300	30	
	Sn - Tin	6000	600	60	
	Cr - Chromium	11000	1100	3	

- Class 1 elements: Toxic and must always be controlled.
- Class 2A: Potentially toxic; likely present from catalysts or processing.
- Class 2B: Used as catalysts but less likely to be present.
- Class 3: Low toxicity by the oral route; less concern for oral meds.

MAXIMUM PERMITTED CONTENT (MPC) OF ELEMENTAL IMPURITIES IN MG/KG (PPM)

Element	Oral PDE (µg/day)	**MPC (mg/kg)** at 10 g/day
Arsenic (As)	**15**	**1.5**
Cadmium (Cd)	**5**	**0.5**
Lead (Pb)	**5**	**0.5**
Mercury (Hg)	**3**	**0.3**
Cobalt (Co)	50	5
Nickel (Ni)	20	2
Vanadium (V)	10	1
Chromium (Cr)	1100	110
Copper (Cu)	3,000	300
Tin (Sn)	6,000	600
Manganese (Mn)	12,000	120
Zinc (Zn)	13,000	1300
Silver (Ag)	167	16
Platinum (Pt)	108	10
Palladium (Pd)	100	10
Ruthenium (Ru)	100	10
Osmium (Os)	100	10
Iridium (Ir)	100	10
Antimony (Sb)	100	10
Barium (Ba)	1400	140

To express the **Maximum Permitted Content (MPC)** of elemental impurities in **mg/kg (ppm)** in pharmaceutical products, we need to convert the **daily PDE (µg/day)** into a concentration, based on the **daily dose** of the drug product.

$$\text{MPC (mg/kg)} = \frac{\text{PDE (µg/day)}}{\text{Maximum Daily Dose (g/day)}} \div 1000$$

The PDE is divided by the maximum daily dose (in grams) to get the concentration in **µg/g**, then divided by 1000 to convert it to **mg/kg** (since 1 µg/g = 1 mg/kg).

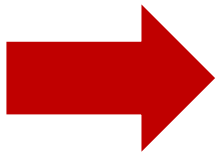
METHOD DESCRIPTION

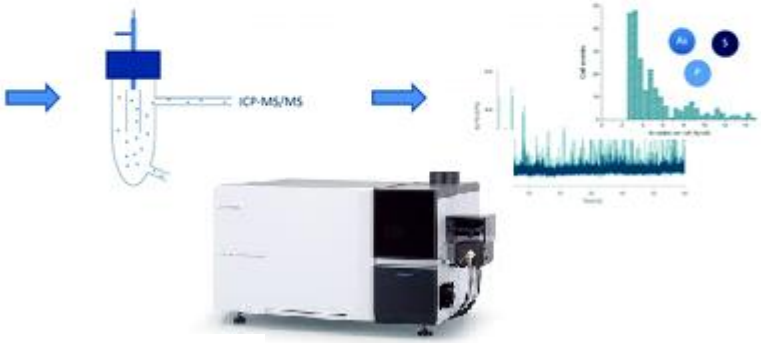
Analytical techniques used

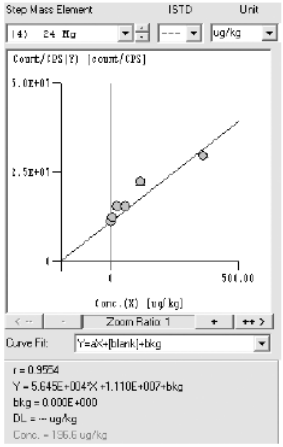
- ICP-MS is the most commonly used method due to its **high sensitivity**, especially for **toxic elements at very low concentrations (ppb or ppt levels)**.

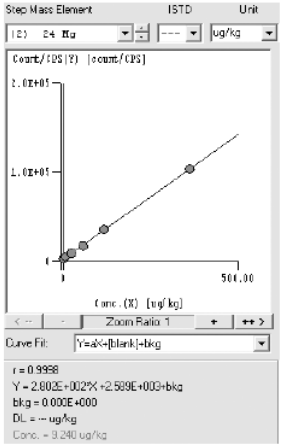
Method	Strengths
ICP-MS (Mass Spec)	High sensitivity, multi-element detection, low LODs
ICP-OES (Optical)	Good for higher concentration ranges, less interference
AAS (Atomic Absorption)	Simple but limited to single-element analysis

SAMPLES PREPARATION



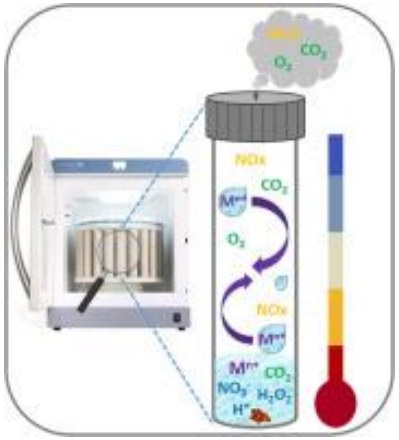






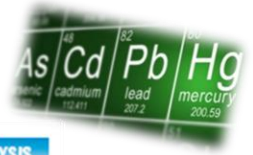
METHODOLOGICAL AND ANALYTICAL CHALLENGES

- **Sample Preparation Variability**: The diverse chemical compositions of pharmaceutical matrices necessitate tailored digestion methods.
- For instance, a study developed a microwave-assisted acid digestion method using aqua regia, followed by a two-step dilution to stabilize elements like osmium (Os), selenium (Se), and gold (Au), which are prone to instability during analysis

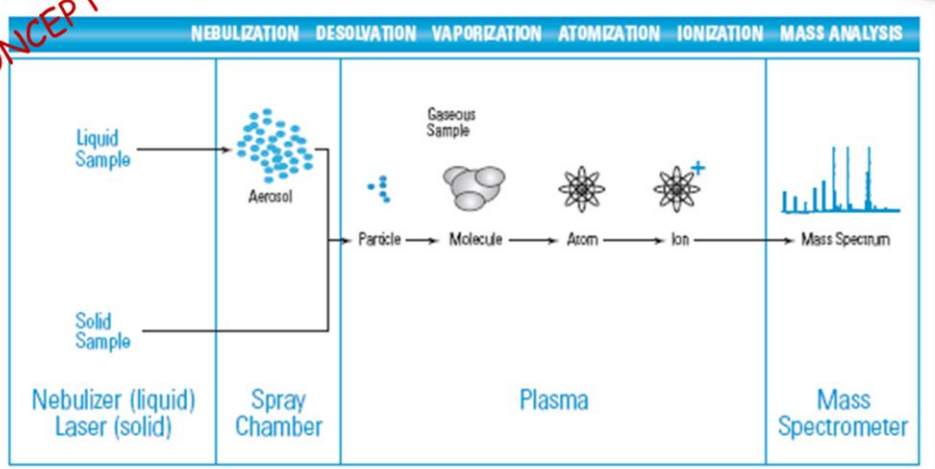


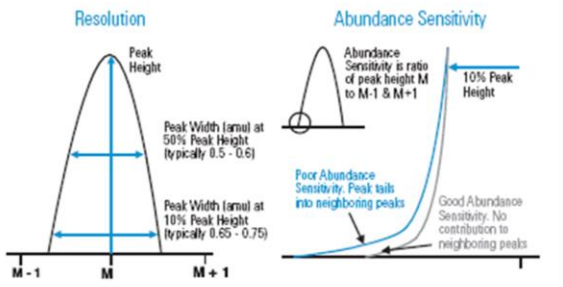
METHODOLOGICAL AND ANALYTICAL CHALLENGES

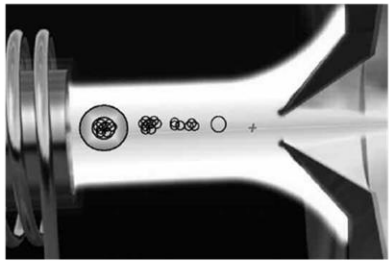
Isotopes measurements



BASIC CONCEPT

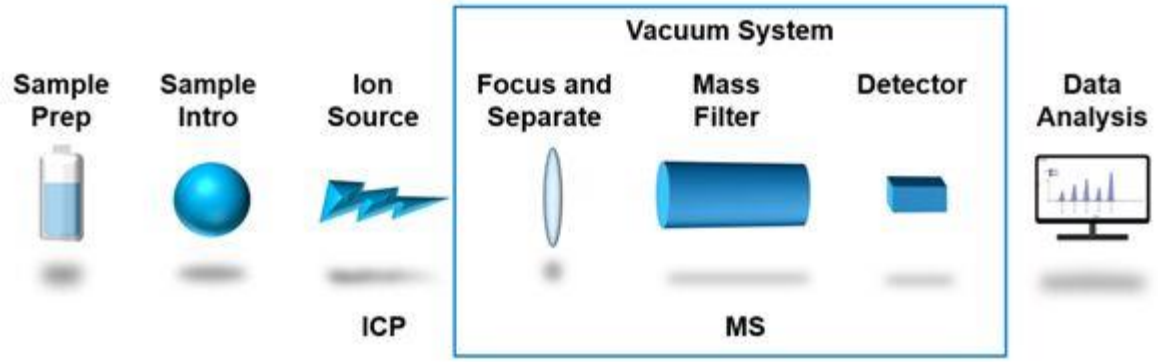






METHODOLOGICAL AND ANALYTICAL CHALLENGES

- **Matrix effects and interferences**: Pharmaceutical samples often contain complex matrices that can cause matrix-induced interferences, such as polyatomic ions (e.g., ArCl+ affecting arsenic detection).
- Utilizing helium (He) collision/reaction cell (CRC) mode in ICP-MS helps mitigate these interferences, enhancing accuracy .



VALIDATION AND COMPLIANCE

ICP-MS methods must undergo rigorous validation to meet regulatory standards:

- **USP <233> Compliance**: Methods should demonstrate linearity, accuracy, precision, and low limits of detection/quantification (LOD/LOQ) for all targeted elemental impurities.
- **Element stabilization**: For elements like mercury (Hg), stabilization in hydrochloric acid (HCl) is necessary to prevent volatilization during digestion
- **Method Ttransfer and verification**:Validated methods must be transferable across laboratories and equipment, ensuring consistent results in quality control settings.

CHALLENGES IN CONTROLLING ELEMENTAL IMPURITIES

ICP-MS Interferences for As, Cd, Hg, and Pb

Element	Isotope	Common Interferences	Source of Interference	Mitigation Strategy
Arsenic (As)	75	$ArCl^+$ (mass 75)	High Cl in matrix (e.g., HCl, NaCl) forms $ArCl^+$ ($^{40}Ar^{35}Cl^+$)	Use He or H_2 collision/reaction cell (CRC), or high-resolution ICP-MS
Cadmium (Cd)	111, 114	MoO^+ (mass 111, 114)	Molybdenum from steel or reagents can form MoO^+	Use collision gas, select less-interfered isotope (e.g., 114Cd), and/or mathematically correct
Mercury (Hg)	202, 200, 201	WO^+ (mass 202)	Tungsten oxide (from labware or contamination)	Use chemical stabilization (HCl) to prevent volatility, and monitor multiple isotopes
Lead (Pb)	208, 206, 207	No major isobaric interferences, but background at high m/z	Matrix components may cause polyatomic species, especially with organics	Use He mode, proper blank correction, and matrix-matched standards

- ICP-MS (Inductively Coupled Plasma Mass Spectrometry) is a powerful tool for detecting trace elements like As, Cd, Hg, and Pb, but it's not without challenges—spectral and non-spectral interferences can affect accuracy.

CHALLENGES IN CONTROLLING ELEMENTAL IMPURITIES

General strategies to minimize interference in ICP-MS

1. **Collision/Reaction cell technology**:
    1. Use **Helium (He)** to remove polyatomic interferences through kinetic energy discrimination.
    2. Use **Hydrogen (H_2) or Oxygen (O_2)** as reaction gases to chemically remove specific interferences.
2. **Isotope selection**:
    1. Choose isotopes with **least interference**.
    2. For example: Cd-114 over Cd-111 when Mo is present.
3. **Matrix matching & internal standards**:
    1. Match standards and samples in acid content and matrix to reduce matrix effects.
    2. Add internal standards like **Bi, In, Rh, or Sc** to correct for drift and suppression.
4. **Chemical stabilization**:
    1. **Mercury** and **osmium** can be volatile; add **HCl** or **aqua regia** to stabilize them in solution.
5. **Use of high-purity reagents**:
    1. Impurities in reagents can introduce background interference.

MONITORING

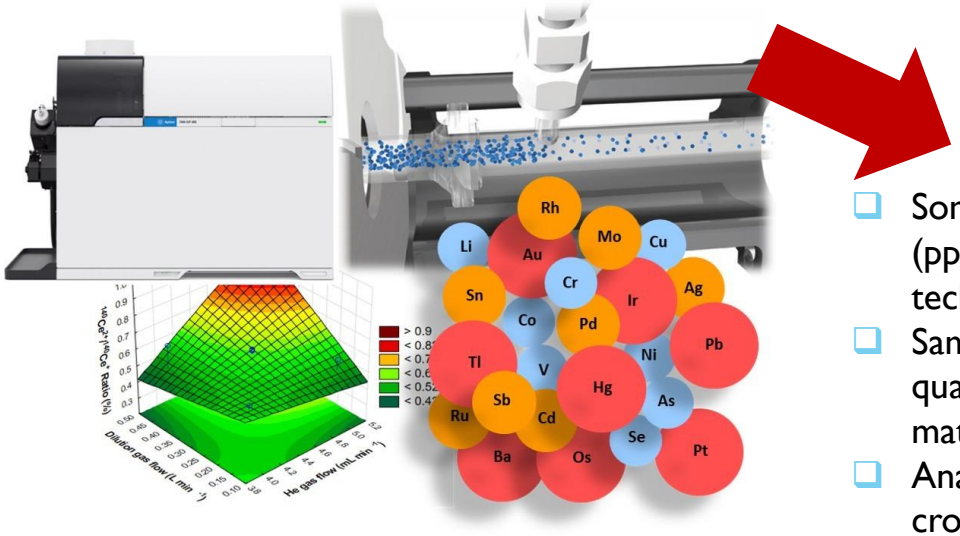
Total of 355 samples has been included in the monitoring, analyzed during the period of January 2023 to January 2025, including:

- Active substance
- Placebo
- Final product

Element	Final pharma product	Placebo	Active substance
Cd	<0.0001 - 0.77	<0.0001 - 0.62	<0.0001 - 0.014
Pb	<0.001- 2.92	<0.001 - 1.33	<0.001 - 0.27
As	<0.0001 - 0.34	<0.0001 - 0.051	<0.0001 - 0.051
Hg	<0.001 - 0.22	<0.001 - 0.028	<0.001 - 0.028
Content given in mg/kg			

PERSPECTIVES

- Identifying all potential sources: A thorough understanding of the full supply chain is required.
- Control strategy development: Must be product-specific and based on risk—this is not a one-size-fits-all situation.
- Cross-contamination: Especially in shared facilities, even low levels of elemental contamination can exceed limits.



- Some elemental impurities are present at trace levels (ppb or lower), requiring highly sensitive analytical techniques like ICP-MS
- Sample matrices can interfere with accurate quantification, requiring rigorous method validation and matrix matching.
- Analyzing multiple elements simultaneously without cross-interference is complex.

ICNTC CONFERENCE

INTERNATIONAL CONFERENCE ON NEW TRENDS IN CHEMISTRY

THANK YOU FOR YOUR ATENTIONE!

www.unilab.ugd.edu.mk

www.ugd.edu.mk

УНИВЕРЗИТЕТ ГОЦЕ ДЕЛЧЕВ
Избери мудро, делувај храбро