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# Application News

## No.J99A

Inductively Coupled Plasma Atomic Emission Spectrometry

# Analysis by ICP Atomic Emission Spectrometry in Accordance with the ICH Q3D Guideline for Elemental Impurities Using ICPE-9820

## Introduction

Analysis of elemental impurities is one of the safety assessments required in the field of pharmaceuticals. In Japan, residual metal catalysts are classified as inorganic impurities according to the guidelines for Impurities in New Drug Substances (No. 1216001, issued by the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau, the Japanese Ministry of Health, Labour and Welfare), and are to be detected appropriately according to the method specified in the Japanese Pharmacopoeia, and evaluated at the stage of drug development. At the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH, various guidelines were established and harmonized between Japan, Europe, and the US, including guidelines for elemental impurities in pharmaceuticals, referred to as the ICH Q3D, Guideline for Elemental Impurities.

For the analysis of elemental impurities, the methods specified for use as general analytical methods in the First Supplement of the Sixteenth Edition of the Japanese Pharmacopoeia include inductively coupled plasma atomic emission spectrometry (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS), and atomic absorption spectrometry. Of these, ICP-AES is the most convenient, offering quick and easy multi-element analysis, and low running costs.

Here, we conducted analysis of 24 elements according to the ICH Q3D guidelines using the Shimadzu ICPE-9820 multi-type ICP atomic emission spectrometer. The ICPE-9820 offers simultaneous all element analysis with high sensitivity and high precision, while delivering high throughput. Low running costs are achieved by a unique combination of the reduced-flow mini-torch and vacuum optics, thereby reducing the overall consumption of argon.

## Outline of the ICH Q3D Guideline for Elemental Impurities

In the ICH Q3D Guideline for Elemental Impurities, 24 elemental impurities were identified as elements of concern due to their toxicity, and permitted daily exposure limits (PDE) were established. The elements include lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As), referred to as the "big four," as well as residual metal catalysts added intentionally in the synthesis of a drug substance. Table 1 shows the ICH Q3D Guideline (STEP4).

As permitted exposure values for the elemental impurities have been set as PDE values, the PDE values must be converted to concentrations to evaluate the elemental impurity components in the formulations or their component substances. As calculation methods, options 1, 2a, 2b, and 3 are available. Therefore, as long as the formulation is appropriate for the PDE value of the elemental impurity, any of the methods may be selected. Calculation examples for the respective options are shown in Table 2 to Table 5.

**Table 1 Permitted Daily Exposure for Elemental Impurities of ICH Q3D (STEP4)**

| Class | Element | Oral µg/day | Parenteral µg/day | Inhalation µg/day | Class | Element | Oral µg/day | Parenteral µg/day | Inhalation µg/day |
|---|---|---|---|---|---|---|---|---|---|
| 1 | As | 15 | 15 | 2 | 2B | Pt | 100 | 10 | 1 |
| | Cd | 5 | 2 | 2 | | Se | 150 | 80 | 130 |
| | Hg | 30 | 3 | 1 | | Rh | 100 | 10 | 1 |
| | Pb | 5 | 5 | 5 | | Ru | 100 | 10 | 1 |
| 2A | Co | 50 | 5 | 3 | | Tl | 8 | 8 | 8 |
| | Ni | 200 | 20 | 5 | 3 | Ba | 1400 | 700 | 300 |
| | V | 100 | 10 | 1 | | Cr | 11000 | 1100 | 3 |
| 2B | Ag | 150 | 10 | 7 | | Cu | 3000 | 300 | 30 |
| | Au | 100 | 100 | 1 | | Li | 550 | 250 | 25 |
| | Ir | 100 | 10 | 1 | | Mo | 3000 | 1500 | 10 |
| | Os | 100 | 10 | 1 | | Sb | 1200 | 90 | 20 |
| | Pd | 100 | 10 | 1 | | Sn | 6000 | 600 | 60 |

**Table 2 Calculation by Option 1: Maximum Permitted Common Concentration Limits of Elemental Impurities Across Drug Product Components for Products with Daily Intake of Not More Than 10 Grams**

| Component Substance | Max. Daily Intake of Each Substance (g) | PDE (µg) | | Max. Permitted Concentration Assuming a 10 g Max. Daily Intake of Formulation (µg/g) | | Max. Intake from Each Component (µg) | |
|---|---|---|---|---|---|---|---|
| | | | | PDE/10 g | | Max. Daily Intake (g) of Each Component × Max. Permitted Concentration (µg/g) of Each Component | |
| | | Pb | As | Pb | As | Pb | As |
| Drug substance | 0.2 | 5 | 15 | 0.5 | 1.5 | 0.1 | 0.3 |
| MCC | 1.1 | 5 | 15 | 0.5 | 1.5 | 0.55 | 1.65 |
| Lactose | 0.45 | 5 | 15 | 0.5 | 1.5 | 0.225 | 0.68 |
| Calcium phosphate | 0.35 | 5 | 15 | 0.5 | 1.5 | 0.175 | 0.53 |
| Crospovidone | 0.265 | 5 | 15 | 0.5 | 1.5 | 0.133 | 0.4 |
| Magnesium stearate | 0.035 | 5 | 15 | 0.5 | 1.5 | 0.018 | 0.05 |
| HPMC | 0.06 | 5 | 15 | 0.5 | 1.5 | 0.03 | 0.09 |
| Titanium oxide | 0.025 | 5 | 15 | 0.5 | 1.5 | 0.013 | 0.04 |
| Iron oxide | 0.015 | 5 | 15 | 0.5 | 1.5 | 0.008 | 0.02 |
| Max. Daily Intake (Total) | 2.5 | | | | | 1.25 | 3.75 |
| PDE (µg/day) | | | | | | 5.0 | 15 |

**Table 3 Calculation by Option 2a: Maximum Permitted Common Concentration Limits Across Drug Product Component Materials for a Product with a Specified Daily Intake (Assuming That Concentration Remains Constant)**

| Component Substance | Max. Daily Intake of Each Substance (g) | PDE (µg) | | Max. Permitted Concentration (µg/g) | | Max. Intake from Each Component (µg) | |
|---|---|---|---|---|---|---|---|
| | | | | PDE/Max. Daily Intake of Actual Drug (e.g. 2.5 g) | | Max. Daily Intake (g) of Each Component × Max. Permitted Concentration (µg/g) of Each Component | |
| | | Pb | As | Pb | As | Pb | As |
| Drug substance | 0.2 | 5 | 15 | 2 | 6 | 0.4 | 1.2 |
| MCC | 1.1 | 5 | 15 | 2 | 6 | 2.20 | 6.6 |
| Lactose | 0.45 | 5 | 15 | 2 | 6 | 0.9 | 2.7 |
| Calcium phosphate | 0.35 | 5 | 15 | 2 | 6 | 0.7 | 2.1 |
| Crospovidone | 0.265 | 5 | 15 | 2 | 6 | 0.53 | 1.59 |
| Magnesium stearate | 0.035 | 5 | 15 | 2 | 6 | 0.07 | 0.21 |
| HPMC | 0.06 | 5 | 15 | 2 | 6 | 0.12 | 0.36 |
| Titanium oxide | 0.025 | 5 | 15 | 2 | 6 | 0.05 | 0.15 |
| Iron oxide | 0.015 | 5 | 15 | 2 | 6 | 0.03 | 0.09 |
| Max. Daily Intake (Total) | 2.5 | | | | | 5.0 | 15 |
| PDE (µg/day) | | | | | | 5.0 | 15 |

**Table 4 Calculation by Option 2b: Maximum Permitted Common Concentration Limits Across Drug Product Component Materials for a Product with a Specified Daily Intake (Arbitrary Setting of Maximum Concentration Possible from Actual Value)**

| Component Substance | Max. Daily Intake of Each Substance (g) | PDE (µg) | | | | Measured Concentration Value (µg) | | | | Arbitrary Setting of Max. Concentration Possible from Actual Value (µg/g) | | | | Max. Daily Intake of Each Componen (µg) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Pb | As | Pd | Ni | Pb | As | Pd | Ni | Pb | As | Pd | Ni | Pb | As | Pd | Ni |
| Drug substance | 0.2 | 5 | 15 | 100 | 200 | ** | 0.5 | 20 | 50 | ** | 5 | 500 | 200 | ** | 1 | 100 | 40 |
| MCC | 1.1 | 5 | 15 | 100 | 200 | 0.1 | 0.1 | * | ** | 0.5 | 5 | * | ** | 0.55 | 5.5 | * | ** |
| Lactose | 0.45 | 5 | 15 | 100 | 200 | 0.1 | 0.1 | * | ** | 0.5 | 5 | * | ** | 0.225 | 2.3 | * | ** |
| Calcium phosphate | 0.35 | 5 | 15 | 100 | 200 | 1 | 1 | * | 5 | 5 | 5 | * | 200 | 1.75 | 1.8 | * | 70 |
| Crospovidone | 0.265 | 5 | 15 | 100 | 200 | 0.1 | 0.1 | * | ** | 0.5 | 5 | * | ** | 0.132 | 1.3 | * | ** |
| Magnesium stearate | 0.035 | 5 | 15 | 100 | 200 | 0.5 | 0.5 | * | 0.5 | 5 | 10 | * | 50 | 0.175 | 0.4 | * | 1.75 |
| HPMC | 0.06 | 5 | 15 | 100 | 200 | 0.1 | 0.1 | * | ** | 2.5 | 5 | * | ** | 0.15 | 0.3 | * | ** |
| Titanium oxide | 0.025 | 5 | 15 | 100 | 200 | 20 | 1 | * | ** | 40 | 20 | * | ** | 1 | 0.5 | * | ** |
| Iron oxide | 0.015 | 5 | 15 | 100 | 200 | 10 | 10 | * | 50 | 20 | 100 | * | 200 | 0.3 | 1.5 | * | 3 |
| Max. Daily Intake (Total) | 2.5 | | | | | | | | | | | | | 4.3 | 14.5 | 100 | 115 |
| PDE (µg/day) | | | | | | | | | | | | | | 5 | 15 | 100 | 200 |

*: Since it has been determined that there is no possibility of Pd being present, a quantitative result is not obtained.
**: Below the detection limit

**Table 5 Calculation by Option 3: Finished Product**
**Concentration (µg/g) = PDE (µg/day)/Daily intake of drug product (g/day)**

| | | PDE (µg) | | | | Maximum Permitted Concentration (µg/g) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Daily Intake (g) | Pb | As | Pd | Ni | Pb | As | Pd | Ni |
| Drug Product | 2.5 | 5 | 15 | 100 | 200 | 2 | 6 | 40 | 80 |

## Sample

· Ophthalmic solution
· Tablet (Daily intake: 1 tablet (0.2 g))

## Sample Preparation

1. Pretreatment of sample (ophthalmic solution)

To 2 mL of sample (approximately 2 g), add 0.5 mL hydrochloric acid, 0.5 mL nitric acid and internal standard element Y (0.5 mg/L based on measurement solution concentration). Adjust the volume to 10 mL using distilled water to use as the measurement solution (5-fold dilution). A spike-and-recovery test solution was prepared using a similarly prepared solution spiked with a standard solution of the measurement element.

2. Pretreatment of tablet sample

Two tablets (daily dosage of 1 tablet per day (0.20 g)) were dissolved with 3 mL hydrochloric acid and 2 mL nitric acid using a microwave sample preparation system and a sample pretreatment quartz vessel.
After conducting microwave digestion, the solution volume was adjusted to 20 mL with distilled water to use as the measurement solution (50-fold dilution). At this time, the internal standard elements Y and In (Y at 0.5 mg/L and In at 1.0 mg/L) were added to the solution. Also, prior to digestion, the measurement element was added to prepare a spike-and-recovery test solution.

## Instrument and Analytical Conditions

Measurement was conducted using the Shimadzu ICPE-9820 multi-type ICP atomic emission spectrometer. The measurement conditions are shown in Table 6.
The ICPE-9820 is a spectrometer that uses the latest CCD, permitting simultaneous measurement of all elements and all wavelengths, while its high-sensitivity axial observation permits high-throughput measurement. Further, the high-temperature plasma generated by the mini torch assures high sensitivity with low ionization interference to provide acquisition of accurate values. In addition, the mini-torch plasma produced by low-flowrate argon gas, the Eco mode and the vacuum spectrometer greatly reduce running costs.

**Table 6 Analytical Conditions**

| | |
|---|---|
| Instrument | : ICPE-9820 |
| Radio frequency power | : 1.2 kW |
| Plasma gas Flowrate | : 10 L/min |
| Auxiliary gas Flowrate | : 0.6 L/min |
| Carrier gas Flowrate | : 0.7 L/min |
| Sample introduction | : Nebulizer 10 |
| Misting chamber | : Cyclone chamber |
| Plasma torch | : Mini-Torch |
| Observation | : Axial (AX) / Radial (RD) |

## Analysis

Quantitative analysis of the 24 elements subject to the ICH Q3D guidelines was conducted using the calibration curve-internal standard method, and spike-and-recovery testing was also conducted.

## Analytical Results

Table 7 shows the results of analysis of the ophthalmic solution. The PDE value of the ophthalmic solution was used as the parenteral value. Table 8 shows the results of the tablet analysis. Good results were obtained in the spike-and-recovery testing for each of the samples (Tables 7 and 8[*1]). In addition, the detection limit calculated as the concentration in the sample (Tables 7 and 8[*2]) adequately satisfied the permitted concentrations (Tables 7 and 8[*3]).

## Conclusion

Use of the ICPE-9820 permits quick, accurate analysis of the 24 elements specified in the ICH Q3D guideline.

[References]
1) Impurities in New Drug Substances (No. 1216001, issued by the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau, the Japanese Ministry of Health, Labour and Welfare)
2) First Supplement of the Sixteenth Edition of the Japanese Pharmacopoeia
3) ICH Q3D: Guideline for Elemental Impurities (STEP4)

**Table 7 Analytical Results of Eye Drop**

| Element | PDE value for parenteral | *3 Permitted concentration | Post-treatment concentration | Spike concentration | Measured concentration (Eye drop) | *1 Spike-and-recovery rate | *2 Converted detection limit (3σ) in ophthalmic solution |
|---|---|---|---|---|---|---|---|
| | μg | μg/mL | μg/mL | μg/mL | μg/mL | % | μg/mL |
| As | 15 | 15 | 3 | 1 | <DL | 104 | 0.04 |
| Cd | 2 | 2 | 0.4 | 0.4 | <DL | 101 | 0.0006 |
| Hg | 3 | 3 | 0.6 | 0.3 | <DL | 105 | 0.007 |
| Pb | 5 | 5 | 1 | 0.3 | <DL | 102 | 0.01 |
| Co | 5 | 5 | 1 | 0.3 | <DL | 95 | 0.001 |
| Ni | 20 | 20 | 4 | 0.5 | <DL | 104 | 0.003 |
| V | 10 | 10 | 2 | 0.5 | <DL | 98 | 0.0008 |
| Ag | 10 | 10 | 2 | 0.5 | <DL | 104 | 0.0008 |
| Au | 100 | 100 | 20 | 0.5 | <DL | 99 | 0.006 |
| Ir | 10 | 10 | 2 | 0.5 | <DL | 101 | 0.01 |
| Os | 10 | 10 | 2 | 0.5 | <DL | 103 | 0.006 |
| Pd | 10 | 10 | 2 | 0.5 | <DL | 102 | 0.004 |
| Pt | 10 | 10 | 2 | 0.5 | <DL | 99 | 0.02 |
| Se | 80 | 80 | 16 | 0.5 | <DL | 103 | 0.02 |
| Rh | 10 | 10 | 2 | 0.5 | <DL | 95 | 0.007 |
| Ru | 10 | 10 | 2 | 0.5 | <DL | 103 | 0.003 |
| Tl | 8 | 8 | 1.6 | 0.5 | <DL | 95 | 0.02 |
| Ba | 700 | 700 | 140 | 0.5 | <DL | 96 | 0.0006 |
| Cr | 1100 | 1100 | 220 | 0.5 | <DL | 97 | 0.002 |
| Cu | 300 | 300 | 60 | 0.5 | <DL | 96 | 0.002 |
| Li | 250 | 250 | 50 | 0.5 | <DL | 99 | 0.01 |
| Mo | 1500 | 1500 | 300 | 0.5 | <DL | 100 | 0.003 |
| Sb | 90 | 90 | 18 | 0.5 | <DL | 103 | 0.01 |
| Sn | 600 | 600 | 120 | 0.5 | <DL | 100 | 0.01 |

PDE value for parenteral
Permitted concentration : When 1 mL of the ophthalmic solution is used per day (Option 3 is used when calculating the conversion to the PDE concentration)
Post-treatment concentration : The permitted concentration in the measurement sample after pretreatment of the sample
Spike concentration : Concentration of spiking solution in spike-and-recovery testing
Converted detection limit (3σ) in ophthalmic solution: Detection limit (3σ) in measurement solution × Dilution factor (5)
<DL: Below the detection limit (3σ)

**Table 8 Analytical Results of Tablet**

| Element | PDE value for oral | *3 Permitted concentration | Post-treatment concentration | Spike concentration | Measured concentration (Tablet) | *1 Spike-and-recovery rate | *2 Tablet converted detection limit (3 σ) |
|---|---|---|---|---|---|---|---|
| | μg | μg/g | μg/mL | μg/mL | μg/g | % | μg/g |
| As | 15 | 75 | 1.5 | 0.5 | <DL | 107 | 0.5 |
| Cd | 5 | 25 | 0.5 | 0.1 | <DL | 100 | 0.007 |
| Hg | 30 | 150 | 3 | 1 | <DL | 101 | 0.1 |
| Pb | 5 | 25 | 0.5 | 0.1 | <DL | 98 | 0.07 |
| Co | 50 | 250 | 5 | 1 | <DL | 101 | 0.01 |
| Ni | 200 | 1000 | 20 | 1 | 0.1 | 100 | 0.03 |
| V | 100 | 500 | 10 | 1 | <DL | 103 | 0.01 |
| Ag | 150 | 750 | 15 | 1 | <DL | 104 | 0.02 |
| Au | 100 | 500 | 10 | 1 | <DL | 105 | 0.03 |
| Ir | 100 | 500 | 10 | 1 | <DL | 100 | 0.09 |
| Os | 100 | 500 | 10 | 1 | <DL | 85 | 0.04 |
| Pd | 100 | 500 | 10 | 1 | <DL | 106 | 0.05 |
| Pt | 100 | 500 | 10 | 1 | <DL | 102 | 0.3 |
| Se | 150 | 750 | 15 | 1 | <DL | 108 | 0.3 |
| Rh | 100 | 500 | 10 | 1 | <DL | 101 | 0.1 |
| Ru | 100 | 500 | 10 | 1 | <DL | 100 | 0.03 |
| Tl | 8 | 40 | 0.8 | 0.1 | <DL | 103 | 0.2 |
| Ba | 1400 | 7000 | 140 | 1 | <DL | 102 | 0.003 |
| Cr | 11000 | 55000 | 1100 | 1 | <DL | 101 | 0.02 |
| Cu | 3000 | 15000 | 300 | 1 | <DL | 105 | 0.05 |
| Li | 550 | 2750 | 55 | 1 | <DL | 104 | 0.1 |
| Mo | 3000 | 15000 | 300 | 1 | <DL | 101 | 0.03 |
| Sb | 1200 | 6000 | 120 | 1 | <DL | 105 | 0.1 |
| Sn | 6000 | 30000 | 600 | 1 | <DL | 100 | 0.03 |

PDE value for oral
Permitted concentration : Permitted concentration in daily intake (0.2 g) (Option 3 is used for calculation of conversion from PDE to concentration)
Post-treatment concentration : Permitted limit concentration in measurement solution following sample pretreatment
Spike concentration : Concentration of the added spike-and-recovery test solution
Tablet converted detection limit (3σ): Detection limit (3σ) in measurement solution Dilution factor (50)
<DL: Below the detection limit (3σ)

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