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Application News

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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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