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Application News

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Inductively Coupled Plasma Mass Spectrometry

Analysis of ICH Q3D Guideline for Elemental Impurities in Drug Products Using ICPMS-2030

Outline of ICH Q3D Guideline for Elemental Impurities in Drug Products

The ICH Q3D Guideline for Elemental Impurities sets permitted daily exposures (PDEs) for 24 elemental metal impurities of which toxicity is a concern, including the so-called big four (lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As)), and residual catalyst metals that are added intentionally during active pharmaceutical ingredient synthesis. Table 1 shows the ICH Q3D guideline of PDE for elemental impurities.
The PDE levels shown for metal impurities must be converted to concentrations in order to evaluate the presence of metal impurities in drug products and their components.
We describe an example of analysis of 24 elements included in the ICH Q3D guideline using inductively coupled plasma mass spectrometry.

Sample

・Tablet (daily dose: 1 tablet [0.2 g])

Sample Preparation

After placing one tablet (daily dose: one tablet [0.20 g]), hydrochloric acid 0.5 mL, and nitric acid 5 mL in a quartz decomposition vessel, decomposition was performed using a microwave sample pretreatment system.
After decomposition, hydrochloric acid 0.1 mL was added, the mixture was made up to 20 mL with pure water, and this solution was used for analysis (100-fold dilution). At this point, Sc, Ga, Y, and Te internal standard elements were added (as an analytical solution concentration of 10 µg/L). After decomposition treatment of a sample, the elements to be measured were added to the sample to create a spike-and-recovery test solution.

Instrument and Analytical Conditions

Shimadzu's ICPMS-2030 inductively coupled plasma mass spectrometer was used for analysis. Analytical conditions are shown in Table 2.
In addition to being highly sensitive, the ICPMS-2030 uses a helium gas collision system that greatly reduces the spectral interference caused by argon and chlorine. Use of Eco mode and a mini-torch drastically reduces running costs associated with gas usage, compared to previous ICP-MS systems.

Table 1 Permitted Daily Exposure Levels for Elemental Impurities in ICH Q3D

Class	Element	Oral Preparations µg/day	Injected Preparations µg/day	Inhaled Preparations µg/day	Class	Element	Oral Preparations µg/day	Injected Preparations µg/day	Inhaled Preparations 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 Analytical Conditions

Instrument	: ICPMS-2030
High-frequency output	: 1.2 kW
Plasma gas flowrate	: 8.0 L/min
Auxiliary gas flowrate	: 1.1 L/min
Carrier gas flowrate	: 0.60 L/min
Sample introduction	: Nebulizer 10
Chamber	: Cyclone chamber (electronic cooling)
Plasma torch	: Mini-torch
Collision gas	: He

Analysis

Quantitative analysis and spike and recovery testing were performed for 24 elements included in ICH Q3D guideline. Analyses were performed by the calibration curve method and internal standard method.

Analytical Results

Table 3 shows the analytical results for tablet preparations. Good spike and recovery results were obtained for all samples. Detection limits converted into sample concentrations also met all permitted concentration levels.

Conclusions

We successfully and accurately analyzed 24 elements included in the ICH Q3D guideline in a short period of time using the ICPMS-2030.

[References]
- Guideline for Elemental Impurities in Drug Products (PFSB/ELD Notification No. 4, September 30, 2015) [In Japanese]
- ICH Q3D Guideline for Elemental Impurities (December 16, 2014)
- General Tests, Supplement I to the Japanese Pharmacopoeia Sixteenth Edition

Table 3 Analytical Results for Tablet Preparations

Element	Oral Preparation PDE	*1 Permitted Concentration	*2 Detection Limit Converted for Tablet Preparations (3 σ)	Measured Result (in Tablet Preparation)	Spiked Concentration (in Tablet Preparation)	Spike and Recovery (%)
	µg	µg/g	µg/g	µg/g	µg/g	%
Ag	150	750	0.001	N.D.	0.1	107
As	15	75	0.002	N.D.	0.2	101
Au	100	500	0.001	N.D.	0.2	91
Ba	1400	7000	0.002	0.013	0.2	96
Cd	5	25	0.003	N.D.	0.2	96
Co	50	250	0.0006	N.D.	0.4	101
Cr	11000	55000	0.003	0.017	0.4	104
Cu	3000	15000	0.04	0.15	0.4	102
Hg	30	150	0.006	N.D.	0.2	100
Ir	100	500	0.0005	N.D.	0.2	98
Li	550	2750	0.01	N.D.	0.2	93
Mo	3000	15000	0.001	N.D.	0.2	107
Ni	200	1000	0.003	0.156	0.4	101
Os	100	500	0.007	N.D.	0.2	92
Pb	5	25	0.001	0.003	0.2	105
Pd	100	500	0.006	N.D.	0.2	104
Pt	100	500	0.003	N.D.	0.2	99
Rh	100	500	0.0008	0.003	0.2	101
Ru	100	500	0.002	N.D.	0.2	98
Sb	1200	6000	0.0009	0.007	0.2	98
Se	150	750	0.01	N.D.	0.2	98
Sn	6000	30000	0.002	N.D.	0.2	98
Tl	8	40	0.0005	N.D.	0.2	103
V	100	500	0.002	N.D.	0.4	100

*1: Permitted concentration: PDE level based on a daily intake of 0.2 g, which refers to a permitted concentration for oral preparations.
*2: Detection limit converted for tablet preparations (3 σ): Detection limit in measured solution (3 σ) × Dilution ratio (100)
N.D.: Not detected

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Shimadzu Corporation
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