EMD MILLIPORE

Trace Elemental Analysis

as Applied to USP 232-233 and Analytical workflows

EMD Millipore Corp. is a subsidiary of Merck KGaA, Darmstadt, Germany

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Regulatory Review

USP <231>

For more than a hundred years, heavy metal impurity analysis has been a common requirement in many monographs. For organizations tasked with FDA compliance, this test is regulated under USP <231>.

The current test is a colorimetric procedure based on the precipitation of insoluble metal sulfides. It is a visual comparison with a control prepared from a standard lead solution, and is therefore qualitative.

Today, more than 80% of all active pharmaceutical ingredients sold in the U.S., are manufactured in another part of the world.1 In order to maintain control over quality and safety, more sophisticated and quantitative analytical methods have become necessary.

USP <232> <233>

Effective January 1st, 2018, chapter 231 will be replaced with

USP<232> "Elemental Impurities – Limits"

Specifies two different classes of elements

- Class 1 – As, Cd, Hg and Pb, the 'Big Four' for which testing is obligatory for all drug products
- Class 2 – Elements that need to be monitored or added (as a catalyst for example) during the production process.

Note: Similar limits have been defined in USP<2232> for Dietary Supplements.

USP<233> "Elemental Impurities – Procedure"

Specifies two reference methods as well as instructions for the validation of both limit test and quantitative procedures.

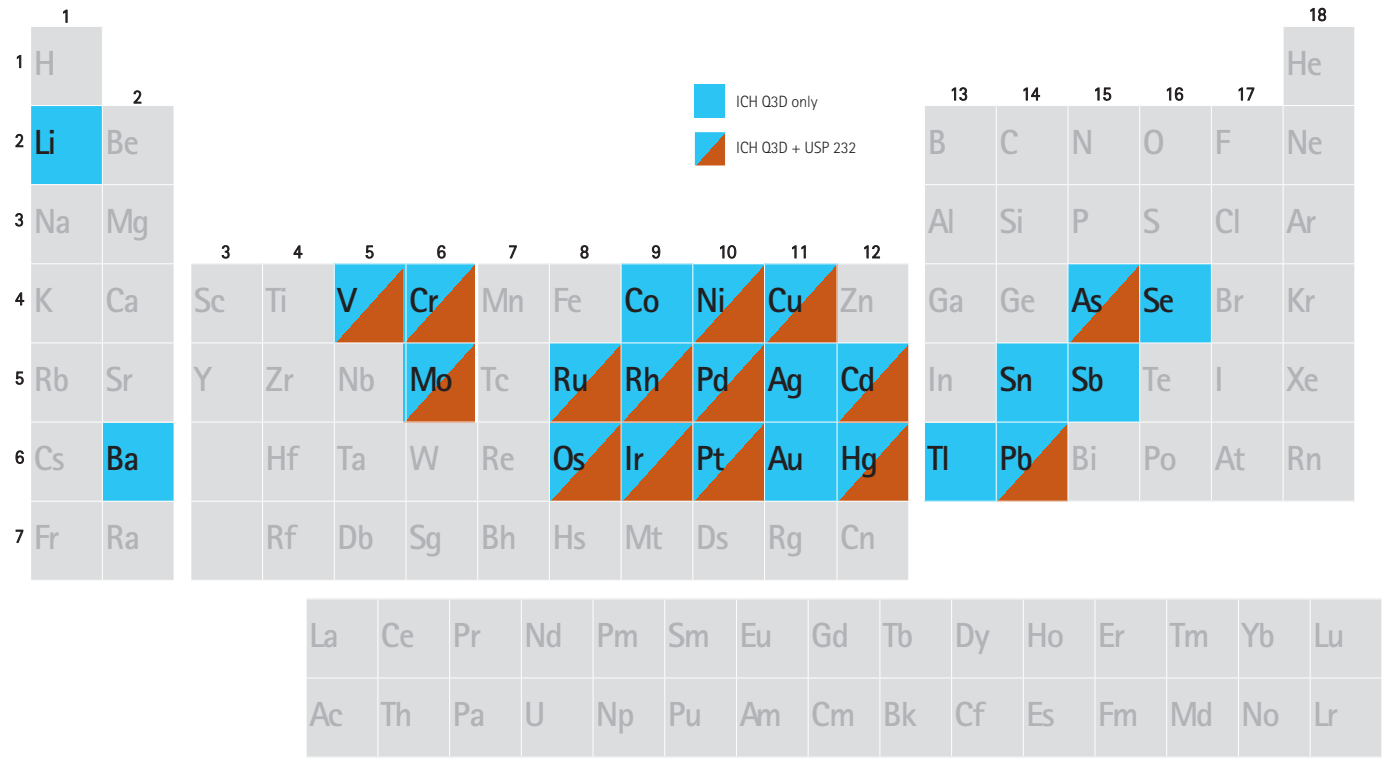
- ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometry)
- ICP-MS (ICP-Mass Spectrometry).

It is important to note that different impurity limits will apply depending on whether the patient dose is parenterally or orally administered. Special Multi-element standards can be utilized when performing calibrations for these types of products.

Regulatory Review

ICH Q3D

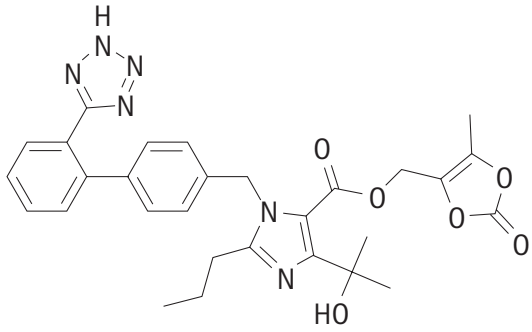
Late in 2014, The International Conference on Harmonization (ICH) issued Guidelines on Elemental Impurities under ICH Q3D. The ICH issued a very comprehensive risk-based guideline for the Pharmaceutical Industry. The FDA, ICH and USP all endeavor to enable globally harmonized regulations. This further benefits global organizations and safety for the world's drug supply. One such area requiring harmonization has to do with the elements of concern as is illustrated in the table below. ICH has some additional elements that are not covered in USP<232>. For this reason, the elemental standards at the end of this literature piece will be identified as applicable for USP <232> or ICH Q3D.



Application by ICP-MS

To demonstrate the application of USP <232>, full parameter testing was performed on a small molecule drug Olmesartan medoxomil following the current pharmacopeial monograph (USP).

Olmesartan medoxomil (USP)



Olmesartan medoxomil is an angiotensin II receptor antagonist. It is an ester prodrug that is completely and rapidly hydrolyzed to the active acid form, olmesartan. It is used to treat high blood pressure.

Common commercial brand names: **Benicar** (US), **Olmetec** (EU, Canada and Japan), **WinBP, Olsar, Golme** (India), etc. **Olmesartan medoxomil** was developed by Daiichi Sankyo in 1995. Patent expires 2016.

ICP-MS (USP 232/233)

- The sample was tested on a high resolution ICP-MS instrument.
- The following metal impurities were measured: Cd, Pb, As, Hg, Ir, Os, Pd, Pt, Rh, Ru, Cu, Mo, Ni, V.
- **Sample Preparation:** 0.1 g sample was digested (closed microwave digestion) in 3 mL HNO3 with 1 mL HCl and 2 mL H202.
- **Calibration (using ICP multi-element standards):**
  For both oral dosage and patenteral dosage the impurities were tested. Thus, the calibration of the HR-ICP-MS was performed for oral and parenteral dosage

Application by ICP-MS

Impurity Limits

Element	Abbreviation	Oral Dose PDE*	Parenteral Dose PDE*
Iridium	IR	100	10
Osmimum	Os	100	10
Palladium	Pd	100	10
Platinum	Pt	100	10
Rhodium	Rh	100	10
Ruthenium	Ru	100	10
Cadmium	Cd	25	2,5
Lead	Pb	5	5
Arsenic	As	1,5	1,5
Mercury	Hg	15	1,5
Copper	Cu	1000	100
Molybdenum	Mo	100	10
Nickel	Ni	500	50
Vanadium	V	100	10

* PDE: Permissable Daily Dose based ona person of 50 kg [µg/day]

- The calibration standards were diluted in either nitric acid or hydrochloric acid.
- For the oral dose the ICP multi-element standards (5.05101.0100 and 5.05103.0100) were used.
- The multi-element standard (5.05101) that contains Cd, Pb, As, Hg, Cu, Mo, Ni and V was diluted in nitric acid.
- The multi-element standard (5.05103) that contains Ir, Os, Pd, Pt, Rh, and Ru was diluted in hydrochloric acid.

- For parenteral dose the ICP multi-element standards 5.05102.0100 and 5.05104.0100 were used.
- The multi-element standard for 5.05102 that contains Cd, Pb, As, Hg, Cu, Mo, Ni and V was diluted in nitric acid.
- The multi-element standard for 5.05104 that contains Ir, Os, Pd, Pt, Rh, and Ru was diluted in hydrochloric acid.

Introducing New Multi-element Standards CertiPur® ICP Standards

- Oral and parenteral dose specific.
- Accredited Production.
- ISO17025 and ISO Guide 34 Compliant.

Ordering Information for products used in this analysis

Description	Catalogue No.
Hydrochloric acid 30% SupraPur®	EM1.00318
Hydrogen peroxide 30% SupraPur®	EM1.07298
Nitric acid 30% SupraPur®	EM1.00441
Elements: As, Cd, Cu, Hg, Mo, Ni, Pb, V	
ICP Multi-element standard USP - I according to USP <232> oral dose Certipur®	EM5.05101
ICP Multi-element standard USP - II according to USP <232> parenteral dose Certipur®	EM5.05102
Elements: Ir, Os, Pd, Pt, Rh, Ru	
ICP Multi-element standard USP - III according to USP <232> oral dose 100 mg/L Certipur®	EM5.05103
ICP Multi-element standard USP - IV according to USP <232> parenteral dose 10 mg/L Certipur®	EM5.05104

Product Selection Guide for ICP-MS for USP<232> <233>

	Product		VWR Cat. No.	Package	Size
Multi-Element ICP Standards USP <232> <2232>	Multi-Element ICP Standard USP I - preparation for oral dose USP <232>		EM5.05101.0100	Plastic Bottle	100ml
	Multi-Element ICP Standard USP II - preparation for parental dose USP <232>		EM5.05102.0100	Plastic Bottle	100ml
	Multi-Element ICP Standard USP III - preparation for oral dose USP <232>		EM5.05103.0100	Plastic Bottle	100ml
	Multi-Element ICP Standard USP IV- preparation for parental dose USP <232>		EM5.05104.0100	Plastic Bottle	100ml
	Multi-Element ICP Standard USP V - dietary supplements for USP <2232>		EM5.02232.0100	Plastic Bottle	100ml
ICP Standards for USP/ ICH Q3D BIG 4	Arsenic ICP standard traceable to SRM from NIST H_3AsO_4 in HNO_3 2-3% 1000 mg/l As Certipur®		EM1.70303.0100	Plastic Bottle	100ml
	Cadmium ICP Standard traceable to SRM from NIST $Cd(NO_3)_2$ in HNO_3 2-3% 1000 mg/l Cd Certipur®		EM1.70309.0100	Plastic Bottle	100ml
	Lead ICP standard traceable to SRM from NIST $Pb(NO_3)_2$ in HNO_3 2-3% 1000 mg/l Pb Certipur®		EM1.70328.0100	Plastic Bottle	100ml
	Mercury ICP standard traceable to SRM from NIST $Hg(NO_3)_2$ in HNO_3 10% 1000 mg/l Hg Certipur®		EM1.70333.0100	Plastic Bottle	100ml
ICP Standards for USP/ ICH Q3D	Chromium ICP standard traceable to SRM from NIST $Cr(NO_3)_3$ in HNO_3 2-3% 10000 mg/l Cr Certipur®		EM1.70374.0100	Plastic Bottle	100ml
	Copper ICP standard traceable to SRM from NIST $Cu(NO_3)_2$ in HNO_3 2-3% 1000 mg/l Cu Certipur®		EM1.70314.0100	Plastic Bottle	100ml
	Iridium ICP standard $IrCl_3$ in HCl 7% 1000 mg/l Ir Certipur®		EM1.70325.0100	Plastic Bottle	100ml
	Molybdenum ICP standard traceable to SRM from NIST $(NH_4)_6Mo_7O_{24}$ in H_2O 1000 mg/l Mo Certipur®		EM1.70334.0100	Plastic Bottle	100ml
	Nickel ICP standard traceable to SRM from NIST $Ni(NO_3)_2$ in HNO_3 2-3% 1000 mg/l Ni Certipur®		EM1.70336.0100	Plastic Bottle	100ml
	Osmium ICP standard $(NH_4)_2OsCl_6$ in HCl 7% 1000 mg/l Os Certipur®		EM1.70338.0100	Plastic Bottle	100ml
	Palladium ICP standard traceable to SRM from NIST $Pd(NO_3)_2$ in HNO_3 2-3% 1000 mg/l Pd Certipur®		EM1.70339.0100	Plastic Bottle	100ml
	Platinum ICP standard traceable to SRM from NIST H_2PtCl_6 in HCl 7% 1000 mg/l Pt Certipur®		EM1.70341.0100	Plastic Bottle	100ml
	Rhodium ICP standard traceable to SRM from NIST $Rh(NO_3)_3$ in HNO_3 2-3% 1000 mg/l Rh Certipur®		EM1.70345.0100	Plastic Bottle	100ml
	Ruthenium ICP standard $RuCl_3$ in HCl 7% 1000 mg/l Ru Certipur®		EM1.70347.0100	Plastic Bottle	100ml
	Vanadium ICP standard traceable to SRM from NIST NH_4VO_3 in HNO_3 2-3% 1000 mg/l V Certipur®		EM1.70366.0100	Plastic Bottle	100ml
ICP Standards for ICH Q3D only	Antimony ICP standard traceable to SRM from NIST Sb_2O_3 in HCl 7% 1000 mg/l Sb Certipur®		EM1.70302.0100	Plastic Bottle	100ml
	Selenium ICP standard traceable to SRM from NIST SeO_2 in HNO_3 2-3% 1000 mg/l Se Certipur®		EM1.70350.0100	Plastic Bottle	100ml
	Tin ICP standard traceable to SRM from NIST $SnCl_4$ in HCl 7% 1000 mg/l Sn Certipur®		EM1.70362.0100	Plastic Bottle	100ml
	Barium ICP standard traceable to SRM from NIST $Ba(NO_3)_2$ in HNO_3 2-3% 1000 mg/l Ba Certipur®		EM1.70304.0100	Plastic Bottle	100ml
	Cobalt ICP standard traceable to SRM from NIST $Co(NO_3)_2$ in HNO_3 2-3% 1000 mg/l Co Certipur®		EM1.70313.0100	Plastic Bottle	100ml
	Gold ICP standard traceable to SRM from NIST $H(AuCl_4)$ in HCl 7% 1000 mg/l Au Certipur®		EM1.70321.0100	Plastic Bottle	100ml
	Lithium ICP Standard traceable to SRM from NIST $LiNO_3$ in HNO_3 2-3% 1000 mg/l Li Certipur®		EM1.70329.0100	Plastic Bottle	100ml
	Silver ICP standard traceable to SRM from NIST $AgNO_3$ in HNO_3 2-3% 1000 mg/l Ag Certipur®		EM1.70352.0100	Plastic Bottle	100ml
	Thallium ICP standard traceable to SRM from NIST $TlNO_3$ in HNO_3 2-3% 1000 mg/l Tl Certipur®		EM1.70359.0100	Plastic Bottle	100ml
High Purity Inorganics for Sample Preparation (FREE Promo Options)	Acetic Acid, 99% Glacial OmniTrace®	- ppb quality	EM-AX0077-1	Poly Coat Glass	500ml
	Ammonium Hydroxide OmniTrace Ultra™	- ppb quality	EM-AX1308-7	HDPE Bottle	250ml
	Boric Acid 99.9999% SupraPur®	- ppb quality	EM1.00765.0050	PE Bottle	50g
	Hydrochloric Acid 30% SupraPur®	- ppb quality	EM1.00318.0500	PE Bottle	500ml
	Hydrochloric Acid 34-37% OmniTrace®	- ppb quality	EM-HX0607-1	Poly Coat Glass	500ml
	Hydrofluoric Acid 40% SupraPur®	- ppb quality	EM1.00335.0500	PE Bottle	500ml
	Hydrofluoric Acid 47-51% OmniTrace®	- ppb quality	EM-HX0627-1	Plastic Bottle	500ml
	Nitric Acid 65% SupraPur®	- ppb quality	EM1.00441.0250	Glass Bottle	250ml
	Perchloric Acid 70% SupraPur®	- ppb quality	EM1.00517.0250	Glass Bottle	250ml
	Sulphuric Acid 96% SupraPur®	- ppb quality	EM1.00714.0250	Glass Bottle	250ml
	Hydrogen Peroxide 30% SupraPur®	- ppb quality	EM1.07298.0250	PE Bottle	250ml
	Water OmniTrace Ultra™	- ppb quality	EM-WX0003-6	LDPE Bottle	1L

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