Reagecon

A CALIBRE SCIENTIFIC COMPANY

Standards for Elemental Impurities in Pharmaceuticals

As Applied to:

ICH Q3D

USP <232>, <233>, <2232>

EP General Test 520 (General Method 2.4.20)

Chinese Pharmacopoeia

Japanese Pharmacopoeia

Indian Pharmacopoeia

Other Pharmacopoeia


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About Reagecon

Reagecon, part of the Calibre Scientific Group of companies is one of the largest producers of Physical and Chemical Standards. The company is based in an 8,000 sq. metre facility that includes a large suite of manufacturing, quality control and research and development laboratories in Shannon, Ireland with sales offices in Shanghai and North America, Europe and the UK through our Calibre Scientific sister companies. Reagecon employs 100 people, 50% are chemistry or science graduates and most are involved in the development, production, testing, quality control and sales & marketing of over 10,000 product references that we currently produce. We have a very active R&D programme and develop and bring to market many hundreds of new standards, every year.

All Reagecon manufactured products are underpinned by and demonstrate our position as a centre of excellence in the science of Metrology. Product is manufactured, tested, and certified under the applicable ISO/IEC 17025 (A2LA Ref: 6739.03) or ISO/IEC 17034 (A2LA Ref: 6739.01) accreditation or ISO/IEC 17025 (A2LA Ref: 6739.02) for Calibration, in one of our 20 specially equipped laboratories.

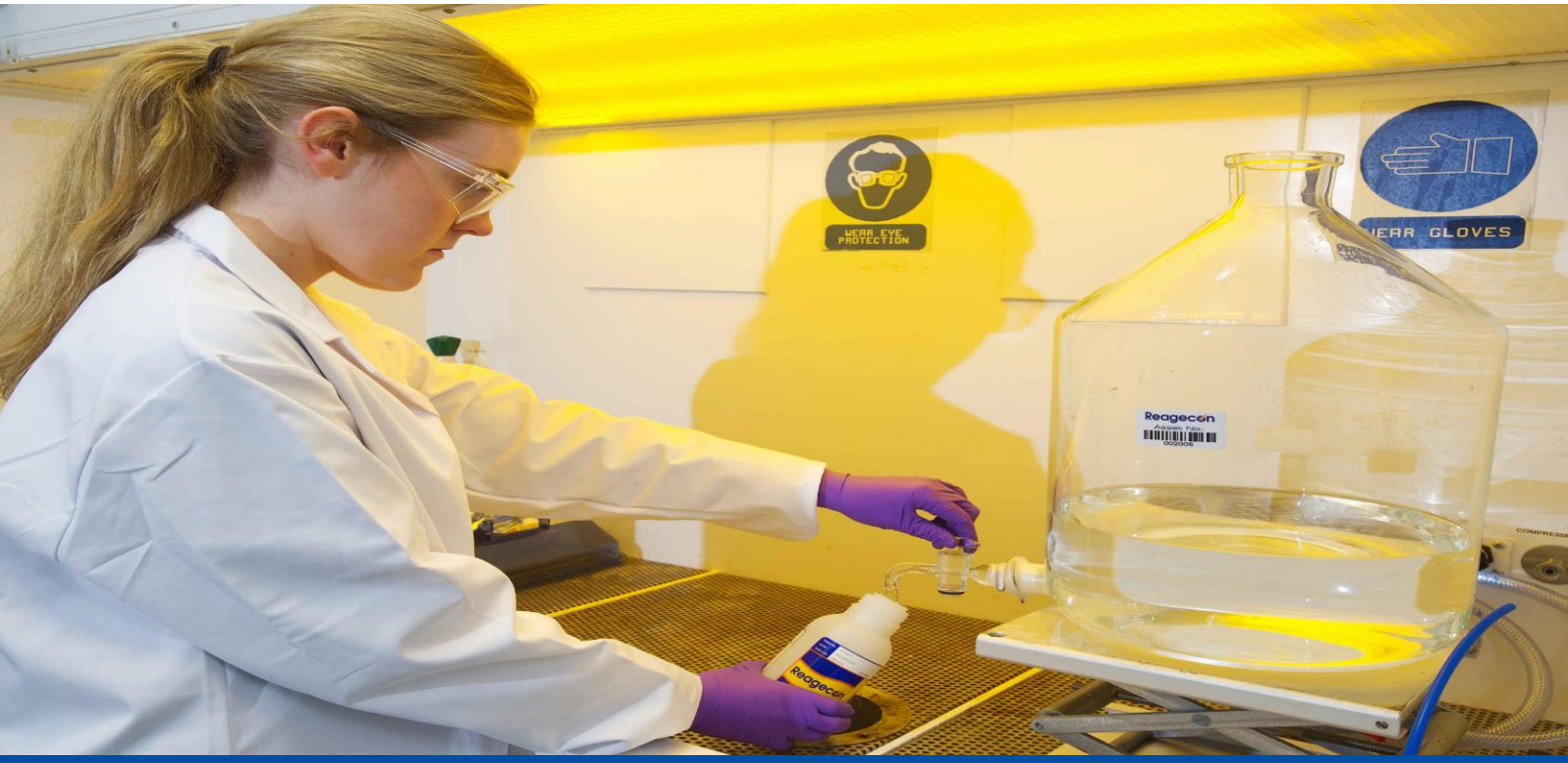
The resulting product is classified within one of 54 product families, these families are then grouped and promoted under 7 main product headings, as listed below:-

- Electrochemistry Standards
- Cation and Anion Standards
- Pharmacopoeia Reagents and Standards
- Physicochemical Standards
- Total Organic and Inorganic Carbon Standards
- Volumetric Solutions for Titration
- Customised Standards and Reagents

History of Elemental Impurities in Pharmaceuticals

The measurement of cations and anions is of critical importance, in almost every industry. In the context of pharmaceutical products, specifically relating to elemental impurities, new standards have been published, that outline procedures for elemental impurities in pharmaceutical products and pharmaceutical ingredients.

More specifically, wet chemistry and spectrophotometric techniques, previously published that include European Pharmacopoeia (EP) Heavy Metal Chapter 2.4.8 and United States Pharmacopoeia Chapter <231>, have now been replaced with instrument-based methods that detail the specific and quantitative determination of individual metal impurities in finished drug products and in ingredients.



New Methods for Impurity Measurement

These new methods are based on the work of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH has published new standards for measuring inorganic impurities in Pharmaceuticals and in their ingredients in a document titled Guideline of Elemental Impurities (Q3D). More specifically, the USP have implemented three new chapters that cover the following:

- Chapter USP <232>: Elemental Impurities in Pharmaceutical Products – Limits
- Chapter USP <233>: Elemental Impurities in Pharmaceutical Products – Procedures
- Chapter USP <2232>: Elemental Contaminants in Dietary Supplements

Similarly, European Pharmacopoeia (EP) have published General Test 5.20 and the general method 2.4.20 in their monograph (9th Edition, supplement 9.3, January 1, 2018) which follows the recommendations of ICH. Furthermore, the EP Commission has recommended keeping the different tests for elements for which no permitted daily exposure (PDE) has been established (see Table 5). These elements have also been identified and published in the ICH Q3D guidelines.

Although most Chinese pharmaceutical companies, already follow ICH Q3D guidelines and limits in their impurity testing, it will be in the new edition of the Chinese Pharmacopoeia, published in 2020 before the ICH Q3D guidelines are incorporated formally into that pharmacopoeia. Japan is already a member of ICH, so it is expected that impurity testing guidelines will be in full compliance with ICH Q3D, even though it is not yet published in the pharmacopoeia.

Similarly, the Indian Pharmacopoeia, does not have an inclusion yet on impurity testing. However, a large number of Indian manufacturers export API materials to countries where EP and USP testing is mandatory, so it's likely that these companies follow ICH Q3D guidelines. Therefore, it seems that methods based on the work of ICH are, or will be, adopted universally and standard mixes presented by Reagecon in Tables 2-5 of this publication are universally applicable.

Context of the New Methods

ICH Method Guidelines for Elemental Impurities (Q3D) includes any inorganic or catalyst elements that may affect a drug product from the following sources:

- Raw materials
- Manufacturing process
- Environment
- Packaging or other container closure systems

The maximum exposure limits are defined according to each impurity's toxicity and route of exposure (see Table 1). USP <233> recommends the use of modern instrumental techniques such as ICP-OES or ICP-MS as the analytical method of choice, although other methods can be used, where it can be demonstrated to meet the necessary performance criteria.

- Parts-per-million (ppm) concentrations ICP-OES or atomic absorption.
- Parts-per-billion (ppb) concentrations ICP-MS

The equivalent method mandated in the most recently published Chinese Pharmacopoeia (ChP) already includes ICP-MS as the recommended analytical technique for determining elemental impurities in pharmaceutical products. As stated, all ICH guidelines will be adapted in the 2020 edition of the ChP

The potential toxicity of an elemental impurity is different depending on the route of exposure. Therefore, elemental impurities must be subjected to risk assessment, which is dependent on the intended route of administration of the finalised drug. Consideration in this risk assessment must be made on the basis of whether the element is naturally present, added intentionally as part of the manufacturing process, added accidently, emanates from a catalytic process, or arises from contamination from equipment or packaging formats.

Hazard Classification (depending on route of ingestion)

Class 1 elements such as Cadmium (Cd), Lead (Pb), Arsenic (As) and Mercury (Hg) must be included in the risk assessment for all drug products, other classes may only need to be considered depending on ingestion route.

The three classes (1-3) are defined on the basis of their toxicity and the likelihood of them occurring in drug products intended for each route of administration. The maximum level of elemental impurities in finalised drug products is expressed as a maximum permitted daily exposure (PDE). PDE takes into account the concentration of the element present in the drug and the maximum recommended daily dose. Specific detail on each ingestion route and the permitted daily exposure limits are presented in Table 1.

Permitted Daily Exposure Limits (depending on route of ingestion)

ICH/USP Class	Element	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (µg/day)
Class 1	Cd – Cadmium	5	2	3
	Pb – Lead	5	5	5
	As – Arsenic (inorganic)	15	15	2
	Hg – Mercury (inorganic)	30	3	1
Class 2A	Co – Cobalt	50	5	3
	V – Vanadium	100	10	1
	Ni – Nickel	200	20	6
Class 2B	Tl – Thallium	8	8	8
	Au – Gold	300	300	3
	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	15	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	1,500	10
	Cu – Copper	3000	300	30
	Sn – Tin	6000	600	60
	Cr - Chromium	11000	1,100	3

Table 1

Reagecon Impurity Standards for Pharmaceutical Products

Reagecon has responded to the changes in the test methods of all the major pharmacopoeias by developing an outstanding and complete range of ultrapure elemental impurity standards. The products are formulated specifically for ICP-OES, ICP-MS or any Atomic Absorption technique. These standards are offered in exactly the concentrations mandated in the pharmacopoeias as being the permitted daily exposure limits (PDE's), depending on ingestions route. Reagecon products can be used for instrument calibration, instrument qualification, quality control or method validation. All of the products are manufactured in an ISO 7 clean room environment, using pure materials (where possible) of either 99.995% or 99.999% purity. The products are certified gravimetrically and verified using a state of the art ICP-MS

Oral Ingestion Standards

ICH/USP/EP	Product No.	Elements	Conc. (µg/mL)	Matrix	Pack Size
Oral Class 1	REAORAL14	Cd - Cadmium Pb - Lead As - Arsenic Hg - Mercury	5 5 15 30	5% HNO3	100mls
Oral Class 2A	REAORAL2A3	Co - Cobalt V - Vanadium Ni – Nickel	50 100 200	2% HNO3	100mls
Oral Class 2B Mix 1	REAORAL2B7M1	Pt - Platinum Au - Gold Pd - Palladium Ir - Iridium Os - Osmium Rh - Rhodium Ru - Ruthenium	100 300 100 100 100 100 100	15% HCl	100mls
Oral Class 2B Mix 2	REAORAL2B3M2	Se - Selenium Ag - Silver Tl – Thallium	150 150 8	2% HNO3	100mls
Oral Class 3 Mix 1	REAORAL34M1	Ba - Barium Cr - Chromium Cu - Copper Li – Lithium	1,400 11,000 3,000 550	10% HNO3	100mls
Oral Class 3 Mix 2	REAORAL33M2	Sb - Antimony Mo - Molybdenum Sn - Tin	1,200 3,000 6,000	5% HNO3, trace tartaric acid, trace HF	100mls

Table 2

Parenteral Ingestion Standards

ICH/USP/EP	Product No.	Elements	Conc. (µg/mL)	Matrix	Pack Size
Parenteral Class 1	REAPAR14	Cd - Cadmium Pb - Lead As - Arsenic Hg – Mercury	2 5 15 3	5% HNO3	100mls
Parenteral Class 2A	REAPAR2A3	Co - Cobalt V - Vanadium Ni – Nickel	5 10 20	2% HNO3	100mls
Parenteral Class 2B Mix 1	REAPAR2B7M1	Pt - Platinum Au - Gold Pd - Palladium Ir - Iridium Os - Osmium Rh - Rhodium Ru – Ruthenium	10 300 10 10 10 10 10	10% HCl	100mls
Parenteral Class 2B Mix 2	REAPAR2B3M2	Se - Selenium Ag - Silver Tl – Thallium	80 15 8	2% HNO3	100mls
Parenteral Class 3	REAPAR37	Li - Lithium Sb - Antimony Ba - Barium Mo - Molybdenum Cu - Copper Sn - Tin Cr - Chromium	250 90 700 1,500 300 600 1,100	2% HNO3, trace tartaric acid, trace HF	100mls

Table 3

Inhalation Ingestion Standards

ICH/USP/EP	Product No.	Elements	Conc. (µg/mL)	Matrix	Pack Size
Inhalation Class 1	REAINHAL14	Cd - Cadmium Pb - Lead As - Arsenic Hg – Mercury	3 5 2 1	5% HNO3	100mls
Inhalation Class 2A	REAINHAL2A3	Co - Cobalt V - Vanadium Ni – Nickel	3 1 6	2% HNO3	100mls
Inhalation Class 2B Mix 1	REAINHAL2B7M1	Pt - Platinum Au - Gold Pd - Palladium Ir - Iridium Os - Osmium Rh - Rhodium Ru – Ruthenium	1 3 1 1 1 1 1	5% HCl	100mls
Inhalation Class 2B Mix 2	REAINHAL2B3M2	Se - Selenium Ag - Silver Tl – Thallium	130 7 8	2% HNO3	100mls
Inhalation Class 3	REAINHAL37	Li - Lithium Sb - Antimony Ba - Barium Na - Sodium Cu - Copper Sn - Tin Cr - Chromium	25 20 300 10 30 60 3	2% HNO3, trace tartaric acid, trace HF	100mls

Table 4

Non-Classified Element Standards

PDE's not yet established (if present in pharmaceutical products, regional guidelines may apply)

ICH/USP/EP	Product No.	Elements	Conc. (µg/mL)	Matrix	Pack Size
Elements not classified	REANC10	Al - Aluminium B - Boron Ca - Calcium Fe - Iron K - Potassium Mg - Magnesium Mn - Manganese No - Nobelium W - Tungsten Zn - Zinc	100 100 100 100 100 100 100 100 100 100	5% HNO3	100mls

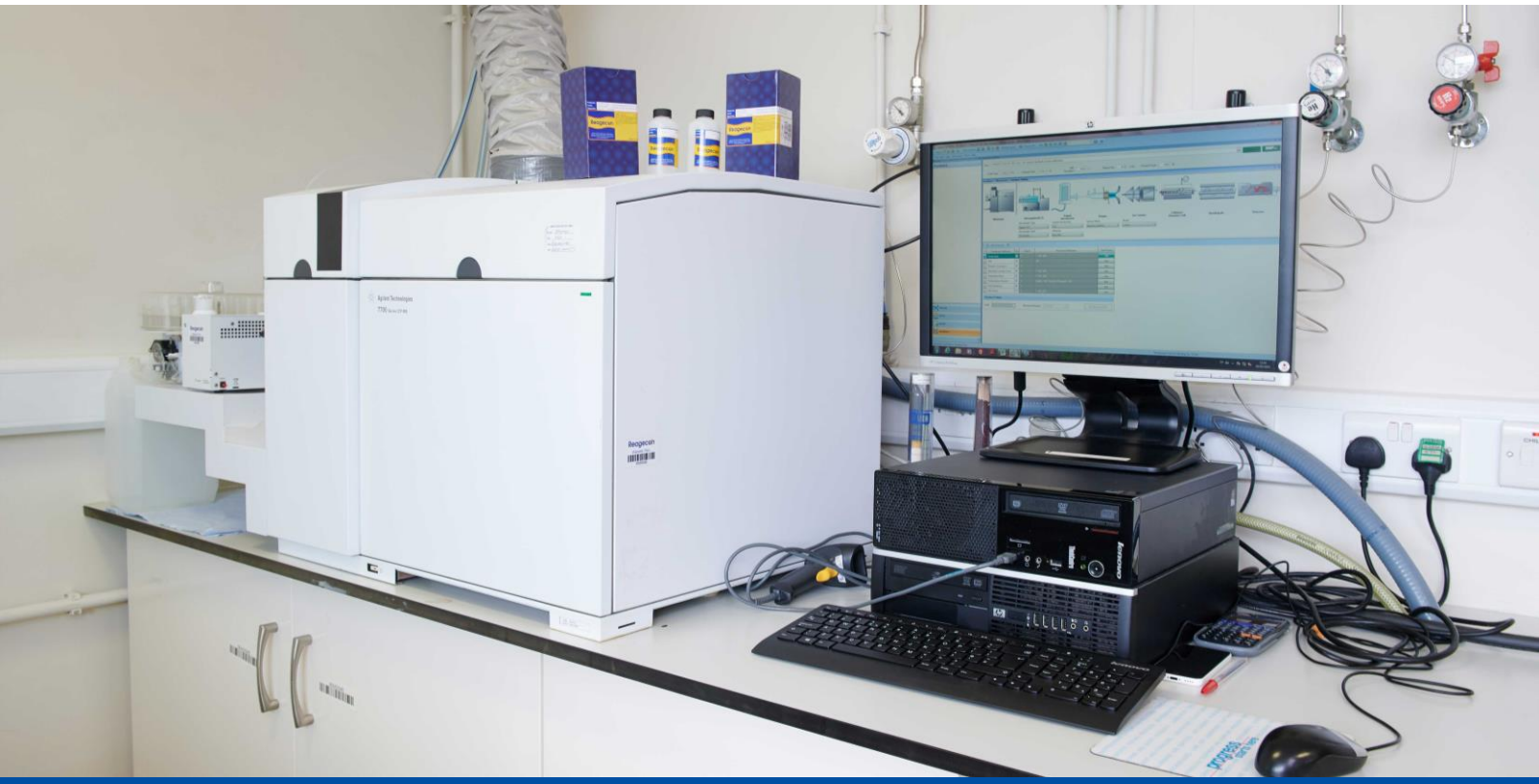
Table 5

Matrix Materials

Reagecon offers a range of Certified High Purity Matrices, specifically produced for trace element analysis. The solutions are produced by sub boiling distillation of ultra-pure starting materials. The products are tested for over 60 different analyte impurities and offer the following features and benefits:

- Extremely low metallic impurities, in most cases less than 10 ppt (parts per trillion).
- Presented in highly resilient fluoropolymer bottles or specially leached glass bottles.
- Supplied with a Certificate of Analysis that contains specifications for over 60 analytes. Certificate shows maximum acceptable levels of impurities for each product as well as the actual result.
- All products are all clearly labelled with the appropriate Hazard and Precautionary (GHS) data in accordance with Health and Safety legislative requirements. The Product Number, Lot Number and Expiry Date are also clearly displayed.

Each bottle is packaged individually and all packaging conforms to International Standards for air and sea transportation in accordance with IATA and IMDG regulations.



Reagecon Certified High Purity Matrix Solutions for Trace Analysis

Product Code	Product Description	Grade	Pack Size
RHPA101	Hydrochloric acid, min 36%	High Purity for Trace Analysis	1L
RHPA102	Nitric acid, min 67%	High Purity for Trace Analysis	1L
RHPA103	Hydrofluoric acid, min 48%	High Purity for Trace Analysis	1L
RHPA104	Sulphuric acid, min 95%	High Purity for Trace Analysis	1L
RHPA105	Perchloric acid, min 68%	High Purity for Trace Analysis	1L
RHPA106	Acetic acid, min 99.5%	High Purity for Trace Analysis	1L
RHPA107	Ammonia solution, min 21%	High Purity for Trace Analysis	1L
RHPA108	Hydrogen peroxide, min 30%	High Purity for Trace Analysis	1L
RHPAX	ASTM Grade 1 Water	High Purity for Trace Analysis	1L

Reagecon's other Cation and Anion Standards

Reagecon offers an extensive range of other standards in both single element and multi element presentation for the following techniques:

- ICP-OES/ICP-MS
- FAAS and GFAAS
- Ion Chromatography
- Flame Photometry
- Ion Selective Electrode

We also offer a competitive range of solutions, reagents and buffers that are manufactured and in full compliance to all the main pharmacopoeias.

For features, benefits, specifications and practical details, visit us at www.reagecon.com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For further information or enquiries, please contact us:

Tel: +353 61 472622
Email: sales@reagecon.ie
www.reagecon.com