(LC)-ICP-MS for elemental analysis in drug development studies. Fully GLP compliant laboratory. Assay validation according to FDA, EMA and ICH guidelines.

(LC)-ICP-MS

- ICP-MS detects elements instead of molecules. With the exception of a few elements (C, H, N, O and the noble gases), all elements can be detected. A specific element serves as a tag for the drug molecule of interest, thus enabling quantitation of this drug molecule in a particular matrix. The technique is highly linear and can be used quantitatively for a broad concentration range. Sample processing is relatively easy and throughput times are short, resulting in fast turnaround times.
- *Total concentration.* Typical Applications of ICP-MS are pharmacokinetic, metabolite profiling, mass balance, pharmacodynamic and toxicology studies. Furthermore, ICP-MS is frequently used for limit testing of elements, trace elemental analysis and formulation analysis.
- *Molecule specific concentration.* ICP-MS extended with HPLC measures the element concentration of all compounds present in the matrix that contain the element of interest and which are chromatographically separated. This combination enables metabolite profiling, and determination of biotransformation and/or degradation products.

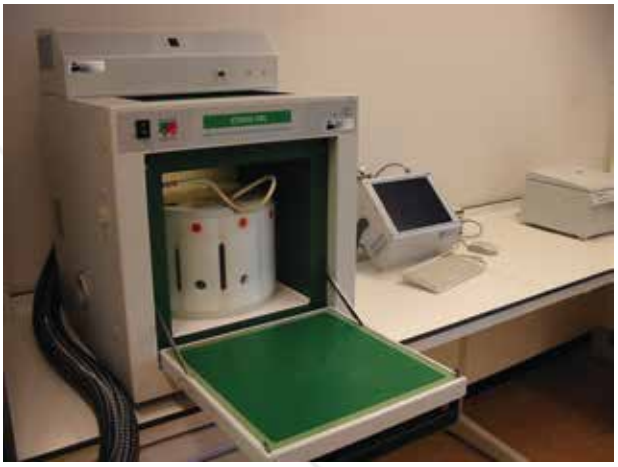
Sample preparation

- Acidic dilution (e.g., plasma, blood, serum, urine, formulation)
- Matrix digestion (e.g., feces, tissue, bone) by:
  - atmospheric disclosure; 2 DigiPREP MS systems
  - pressurized disclosure; 2 Milestone microwave systems
- Ultra-filtration and equilibrium dialysis for determination of free (unbound) drug concentrations
- Solid-phase and liquid extraction

Analytical possibilities

- HPLC separation for quantitation of parent compound and metabolites
- Serial detection using ICP-MS and UV (diode array)
- Parallel detection using ICP-MS and LC-MS/MS
- ELISA-ICP-MS

2x DigiPREP for digestion of 216 samples per run



Microwave-assisted digestion

Why QPS?

- We have built up vast ICP-MS experience since 2004 in method development, validation and quantitation of many elements in various sample species and matrices from (pre-) clinical, R&D and manufacturing origin.
- We have 2 LC-ICP-MS systems and thus sufficient capacity for your studies.
- We have extensive equipment for sample preparation.
- We are very flexible and cooperative, and have broad experience in (bio)analytical chemistry, including regulatory aspects.
- We are used to conducting complex studies.
- We value face to face meetings. You are welcome to visit us and view our laboratory.

(LC)-ICP-MS in drug development

Examples of different elements of interest for ICP-MS related to various applications:

METALLOPEPTIDES

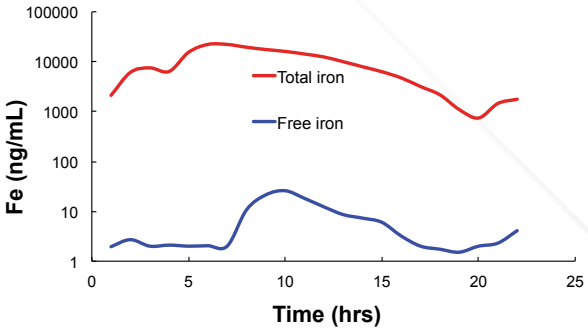
Metalloenzymes:	Cu, Fe, Mg, Mn, Mo, Ni, Se, Zn
Metalloenzymes	
Physiological:	Zn, Cu, Se
Xenobiotic:	Cd, Hg, Ag,...
Phytochelatins:	Cd, Ag, Cu, Pb, Zn
Transport proteins	
Albumin:	Cu, Al; Transferrin: Fe, Al
CorA:	Mg, Co, Fe, Ni

METALLODRUGS

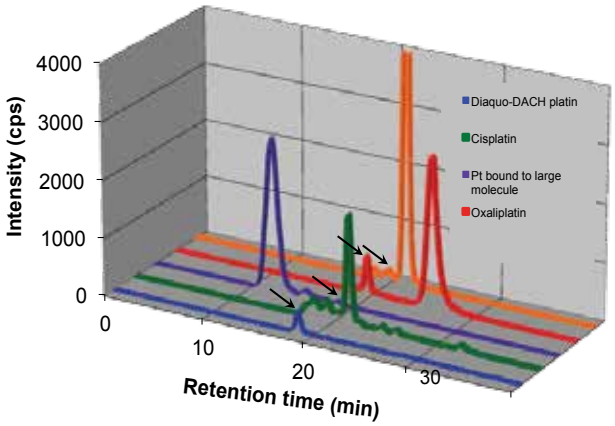
Indazolium, imidazolium:	Ru
Chemotherapeutics:	Pt, Ru, Rh, Ti, Ga, As
Bone resorption:	La, Eu, Gd, Tb, Yb
Anti-arthritic therapeutics:	Au
Anti-diabetes therapeutics:	V, Cr, Cu, Zn, Mn, Mo
Gastrointestinal disorders, stomach ulcer:	Bi, Al

MISCELLANEOUS

DNA restriction fragments:	Fe, Mn, Co, Pb, Cd
Metalloporphyrines:	As(III)/As(V), Ge, Sb, Se, Co(II)/Co(III)
Ferrocene derivatives:	Fe
Cobalamines, cobanamids:	Co
Imaging agents:	Tc, Fe, Gd, Mn, I, Ba
Amino acid-complexed metals:	Zn, Cu, Mn, Ni



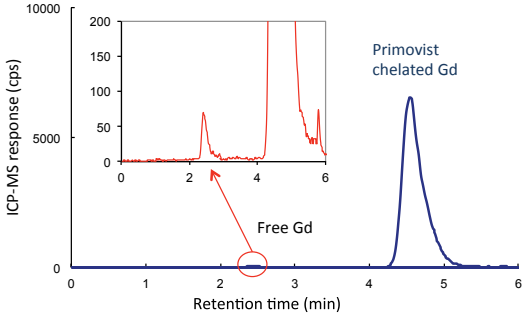
Human serum PK curves of total (protein bound + free) and free iron concentrations after dosage of an iron sucrose compound for screening purposes. Free iron was obtained using ultra-filtration (10 kDa) prior to quantitation by ICP-MS.



Chromatographic separation of platinum compounds, both free and bound to large molecules in a single run. Arrows indicate the Diaquo-DACH platin present as a degradation product in different platinum compounds

Some examples of (LC)-ICP-MS assays developed at QPS

- Determination of free and total platinum in urine, whole blood, red blood cells, or plasma from new or existing platinum drug formulations used in oncolytical studies, e.g., oxaliplatin, cisplatin and carboplatin
- Analysis of micelle and/or protein-bound and free platinum in one analytical run using LC-ICP-MS and size exclusion chromatography
- Simultaneous determination of free and chelated Gd (up to 1 : 10000) in MRI contrast enhancing agents under development to contain lower free Gd concentration (see figure below)
- Determination of platinum in mouse plasma and mouse organs by LC-ICP-MS
- Determination of copper, zinc, aluminum and iron in human blood. These elements play a role in Alzheimer and Parkinson disease and are considered biomarkers



LC-ICP-MS of gadolinium in human plasma. Shown is the chromatographic separation of chelated gadolinium (Primovist at 250 µg/mL) and free gadolinium. Separation was performed using size exclusion chromatography.
With an LLOQ of 10 ng/mL, a concentration ratio of free : bound of 1 : 10000 was obtained.

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